Toxicology Research Laboratory

UIC The University of Illinois at Chicago

Department of Pharmacology (M/C 868)
1940 W. Taylor St.
Chicago, Illinois 60612-7353

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

Title Page

Volume 1 of 3 DRAFT

Draft Report for Task Order No. UIC-5B

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

Sponsor: US Army Medical Materiel Development Activity

Test Article: WR238605

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

June 18, 1993

Performing Laboratory

TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
Chicago, IL 60612-7353

UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

DRAFT

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY Unclassified	3. DISTRIBUTION/AVAILABILITY OF REPORT Unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) UIC-5 (UIC/TRL Study No. 098)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Toxicology Research Laboratory University of Illinois at Chicago 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Research Acquisition Activity
6c. ADDRESS (City, State, and ZIP Code) Department of Pharmacology (M/C 868) 1940 W. Taylor Street Chicago, IL 60612-7353	7b. ADDRESS (City, State, and ZIP Code) ATIN: SGRD-RMA-RCD Fort Detrick Frederick, MD 21702
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Materiel Development Activity 8b. OFFICE SYMBOL (If applicable) SGRD-UMP	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-92-C-2001
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21702-5009	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 63807A; PROJECT NO. 30463807; TASK NO. QC; WORK UNIT ACCESSION NO. 073

11. TITLE (Include Security Classification)
THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

12. PERSONAL AUTHOR(S)
Levine, Barry S.; Tomlinson, Michael J. (Pathology Associates, Inc.)

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
DRAFT	FROM 9/1/92 TO _____		

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	WR 238605; Hemolytic anemia; Toxicology; Antimalarial

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This study evaluated the toxicity of WR238605 in rats following thirteen weeks of daily oral (gavage) administration. A thirteen week recovery period was included for all groups. Dose levels studied were 0 (vehicle control), 0.5, 6 and 18 mg base/kg/day. The primary toxic affects were seen in the RBCs, lungs, and liver. Significant methemoglobin production was observed in mid and high dose animals, but was reversible. Microscopic lesions in the spleen, kidney, and bone marrow were secondary to mild hemolytic anemia. Toxicity again was limited to the two highest dose levels. Decreased food consumption, decreased body weight gains, methemoglobin production and mild anemia were observed at the mid and high dose levels, but were readily reversible after treatment cessation. Increases in serum ALT, AST, and/or LDH and decreased A/G ratios in high dose animals and possibly mid dose males suggested mild hepatotoxicity, however histopathologic lesions were not seen. Leukocytosis possibly secondary to stress and consisting of increased number of lymphocytes, mature neutrophils, and/or monocytes was seen in the treatment period at the two highest dose levels and was reversible after cessation of treatment. Because the aforementioned toxic responses were limited to mid and high dose animals, a no-adverse effect level of WR238605 was assessed to be 0.5 mg base/kg/day.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Barry S. Levine	22b. TELEPHONE (Include Area Code) (312) 996-5543 22c. OFFICE SYMBOL N/A

DD Form 1473, JUN 86 *Previous editions are obsolete.*

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

DRAFT

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 098 entitled "Thirteen Week Oral Toxicity Study of WR238605 with a Thirteen Week Recovery Period in Rats" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

_____ _____

Barry S. Levine, D.Sc., D.A.B.T. Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

STUDY NUMBER: 098

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 9/1/92

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 9/1/92, TO STUDY DIR 9/1/92, TO MGMT 9/1/92
PHASES: PROTOCOL REVIEW
INSPECT ON 12/7/92, TO STUDY DIR 12/8/92, TO MGMT 12/8/92
PHASES: ROOM ENVIRONMENT AND ANIMAL RECEIPT
INSPECT ON 3/9/93, TO STUDY DIR 3/10/93, TO MGMT 3/10/93
PHASES: ANALYTICAL LABORATORY
INSPECT ON 3/18/93, TO STUDY DIR 3/18/93, TO MGMT 3/18/93
PHASES: BLOOD COLLECTION, EUTHANASIA AND NECROPSY
INSPECT ON 9/1/93, TO STUDY DIR 9/2/93, TO MGMT 9/8/93
PHASES: RAW DATA FROM ANALYTICAL LABORATORY
INSPECT ON 9/2/93, TO STUDY DIR 9/2/93, TO MGMT 9/8/93
PHASES: DRAFT REPORT FROM ANALYTICAL LABORATORY
INSPECT ON 9/17-23/93, TO STUDY DIR 9/23/93, TO MGMT 9/27/93
PHASES: RAW DATA
INSPECT ON 9/17/93, TO STUDY DIR 9/17/93, TO MGMT 9/17/93
PHASES: PATHOLOGY DRAFT REPORT
INSPECT ON 9/17/93, TO STUDY DIR 9/17/93, TO MGMT 9/23/93
PHASES: OPHTHAMOLOGY DRAFT REPORT
INSPECT ON 10/13-15/93, TO STUDY DIR 10/15/93, TO MGMT 10/18/93
PHASES: DRAFT FINAL REPORT

Ronald Schoenheck 10/19/93

QUALITY ASSURANCE DATE

DRAFT

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

Signature Page

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

TRL Chemical No.: 0720614

Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
Chicago, IL 60612-7353

_____ _____

Barry S. Levine, D.Sc., D.A.B.T. Date
Study Director

Study Initiation: September 1, 1992
Dosing Initiation: December 17, 1992
In-Life Completion: June 18, 1993

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

TABLE OF CONTENTS

DRAFT

VOLUME 1

TITLE PAGE 1

STATEMENT OF COMPLIANCE 2

QUALITY ASSURANCE STATEMENT 3

SIGNATURE PAGE 4

TABLE OF CONTENTS 5

1. SUMMARY 7

2. INTRODUCTION 7

3. MATERIALS AND METHODS 7

3.1 Test Article 7
3.2 Animals 8
3.3 Experimental Design 8
3.4 Statistical Analyses 12

4. RESULTS 13

4.1 Dosage Formulation Analyses 13
4.2 Mortality and Clinical Signs/Observations 13
4.3 Body Weight 14
4.4 Food Consumption 14
4.5 Clinical Pathology 14
4.6 Ophthalmology 16
4.7 Organ Weights 16
4.8 Pathology 16

5. DISCUSSION/CONCLUSION 17

6. PERSONNEL 19

7. ARCHIVES 19

LIST OF TABLES

1 Summary of Toxic Responses 20
2 Dosage Formulations Analyses 21
3 Male Summary of Clinical Signs 22
4 Female Summary of Clinical Signs 23
5 Male Summary of Body Weights 24
6 Male Summary of Weight Gains 26

DRAFT

TABLE OF CONTENTS (contd.)

LIST OF TABLES (contd.)

7	Female Summary of Body Weights	28
8	Female Summary of Weight Gains	30
9	Male Summary of Daily Food Consumption	32
10	Female Summary of Daily Food Consumption	34
11	Male Summary of Clinical Chemistry Tests	36
12	Female Summary of Clinical Chemistry Tests	54
13	Male Summary of Hematological Tests	72
14	Female Summary of Hematological Tests	91
15	Male Organ Weight Summary (% Body Weight)	110
16	Male Organ Weight Summary (Absolute)	112
17	Female Organ Weight Summary (% Body Weight)	114
18	Female Organ Weight Summary (Absolute)	116
19	Summary of Microscopic Lesions	118

FIGURES

1	Summary of Male Body Weights	119
2	Summary of Female Body Weights	120

VOLUME 2

APPENDICES

1	Analytical Chemistry Report	1-1
2	Clinical Pathology Methodology	2-1
3	Mortality and Individual Observations (Clinical Signs)	3-1
4	Individual Body Weight and Body Weight Gains	4-1
5	Individual Food Consumption Data	5-1
6	Individual Clinical Chemistry Data	6-1

VOLUME 3

APPENDICES (contd.)

7	Individual Hematology Data	7-1
8	Ophthalmology Report	8-1
9	Individual Organ Weights	9-1
10	Pathology Report	10-1
11	Pretest Clinical Pathology Data	11-1
12	Protocol and Protocol Amendments	12-1
13	Study Deviations	13-1

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

1. SUMMARY

This study evaluated the toxicity of WR238605 in rats following thirteen weeks of daily oral (gavage) administration. A thirteen week recovery period was included for all groups. Dose levels studied were 0 (vehicle control), 0.5, 6 and 18 mg base/kg/day. The results are summarized in Table 1. The primary toxic affects were seen in the RBCs, lungs, and liver. Significant methemoglobin production was observed in mid and high dose animals, but was reversible. Microscopic lesions in the spleen, kidney, and bone marrow were secondary to mild hemolytic anemia. Toxicity again was limited to the two highest dose levels. Decreased food consumption, decreased body weight gains, methemoglobin production and mild anemia were observed at the mid and high dose levels, but were readily reversible after treatment cessation. Increases in serum ALT, AST, and/or LDH and decreased A/G ratios in high dose animals and possibly mid dose males suggested mild hepatotoxicity, however histopathologic lesions were not seen. Leukocytosis possibly secondary to stress and consisting of increased number of lymphocytes, mature neutrophils, and/or monocytes was seen in the treatment period at the two highest dose levels and was reversible after cessation of treatment. Because the aforementioned toxic responses were limited to mid and high dose animals, a no-adverse effect level of WR238605 was assessed to be 0.5 mg base/kg/day.

2. INTRODUCTION

This study was conducted to determine the specific target organ toxicity, dose-response relationships and determination of a no-adverse effect level of WR238605 in rats following thirteen weeks of daily oral administration. A thirteen week recovery period was included for all treatment groups to assess the reversibility of toxic effects. The study was conducted in accordance with the specifications of the Sponsor. The rat is a standard and accepted rodent species for regulatory toxicology studies, and was specified by the Sponsor. Oral administration is the intended clinical route and was also specified by the Sponsor. All methods and procedures were conducted in accordance with the Quality Assurance Programs of the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc., designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on December 17, 1992 and the in-life portion was terminated on June 18, 1993.

3. MATERIALS AND METHODS

3.1 Test Article

WR238605 succinate (Bottle No. BM12562), a fine, pale yellow powder, was received on October 5, 1992 from Herner & Co. The chemical name of the test article is 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate and the mole fraction of the base is 0.8. It was stored at 0 - 4°C and ambient humidity, protected from light in an amber bottle.

The Analytical Chemistry Report is contained in Appendix 1. The test article was initially identified by GC-MS and the purity was determined to be greater than 99.9%). The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was also greater than 99.9%. Thus, the test article was stable under storage conditions.

3.2 Animals

One hundred five male and 105 female CD® Virus Antibody Free (VAF) rats were obtained from Charles River Breeding Laboratories (Portage, MI) on December 7, 1992. The animals were approximately 6 weeks old (date of birth October 28, 1992) upon arrival at the UIC AAALAC-accredited animal facility. Each animal was given a study-unique quarantine/pretest number following placement in cages. Animals were singly housed in polycarbonate cages with Anderson bed-o-cob® bedding (Heinold, Kankakee, IL) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, was adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages with fresh bedding weekly.

Purina Certified Rodent Chow No. 5002 (Ralston Purina Company, St. Louis, MO) was provided *ad libitum* from arrival until termination, except during an approximate 16 - 20 hour fast prior to blood collection for clinical pathology and/or necropsy. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum*. The water was untreated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

3.3 Experimental Design

Near the end of the one week quarantine/pretest period, 80 animals of each sex were randomized by sex into the groups shown in the following table using a computer-generated randomization program, stratified on the basis of body weight.

Treatment Group	Dose Level (mg base/kg/day)	Number of Males	Number of Females
1	0	10 + 10*	10 + 10*
2	0.5	10 + 10*	10 + 10*
3	6	10 + 10*	10 + 10*
4	18	10 + 10*	10 + 10*

*Recovery Animals

Dose levels were supplied by the Sponsor based on the results of a 28-day gavage rat study, and were extrapolations from that shorter-term toxicology study.

Ten animals/sex/dose were necropsied in Week 14 after 91 or 92 days of dosing, except in the high dose (due to mortality) as described in Sec 4.2. All remaining animals were held for a thirteen week recovery period, at which time they were necropsied. The number of animals/sex/group was necessary for adequate statistical analysis.

During the test animal selection process, each animal was assigned an animal number unique to it within the population making up the study. This number appeared as an ear tag and also appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, sex, treatment group number, and dose level. Cage cards were color-coded as a function of treatment group.

Dosage formulations were prepared every two weeks by suspending the appropriate quantity of the test article in the vehicle (aqueous 1% methylcellulose/0.4% Tween 80). Stability was based on data from a previously conducted dog toxicity study (UIC/TRL Study No. 047). WR238605 dosage formulations were also shown to homogeneous in that study. A sample of all dosage formulations used in Weeks 1 & 2, 7 & 8, and 13 were analyzed for test article concentration prior to their use. The results of these analyses are included in Table 2 and in Appendix 1.

The test article were suspended in the vehicle to result in concentrations necessary to administer the dosage formulations at a volume of 5 ml/kg. The specific volume (ml) administered was calculated on the basis of each animal's most recent body weight. The quantity of the test article was calculated as mg base/kg/day. The test article dosage formulation was administered by gavage once daily for 91 or 92 days beginning on December 17, 1992 (Day 0). The animals were dosed up to and including the day prior

to scheduled necropsy, except for the recovery animals, which were dosed for 91 days. Control animals received the vehicle (aqueous 1% methylcellulose/0.4% Tween 80). The rats weighed 195 - 260 g (males) and 145 - 190 g (females) on Day 0 and were approximately seven weeks old at initiation of treatment.

Non-fasted body weights were recorded on Day -7, on Day 0 prior to dosing, and weekly thereafter. Fasted body weights were collected at scheduled termination. Clinical signs were recorded once daily, approximately 1 - 2 hours after dosing. The general behavior, posture, locomotion, breathing pattern and coat were observed for all animals. The animals were also observed immediately prior to dosing and in the afternoon for moribundity/mortality. During the recovery period, clinical signs were recorded once daily in the morning. Physical examinations (clinical observations) which included examination of eyes and all orifices were conducted in Week -1, on Day 0 prior to dosing, and once weekly thereafter. Food consumption was measured for all animals weekly commencing with Week -1. All rats were examined by indirect ophthalmoscopy prior to study initiation (Week -1) and during Week 13, and in Week 26 for the recovery animals. The animals were treated with 1% atropine sulfate eye drops prior to the examination.

Hematology and clinical chemistry parameters were measured for 5 rats/sex during the quarantine/pretest period (Appendix 11), and for 10 animals/sex/group during Weeks 2, 4, 8 and 13, and in Weeks 16, 21 and 27 (at necropsy) for the recovery groups. The recovery animals were routinely used throughout the study for these measurements. The overnight fasted animals were anesthetized by carbon dioxide inhalation, and approximately 1.5 - 2.0 ml of blood was collected from the orbital sinus to measure the following parameters. The samples were processed in the same random order as collected. Water was available *ad libitum* during all fasting periods. Clinical pathology methodology is contained in Appendix 2.

Hematology

[a]Erythrocyte count and morphology
Heinz bodies
Hematocrit
Hemoglobin
Leukocyte count, total and differential
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
[b]Methemoglobin
Platelet count
Reticulocyte count

[a]Includes nucleated RBCs.

[b]Measured with a Co-oximeter (Instrumentation Laboratory Model 282). The assay was performed within one hour of sample collection. The specimens were kept on wet ice prior to analysis.

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

Clinical Chemistry

Albumin (A)
Albumin/Globulin (A/G) ratio (calc.)
Alkaline phosphatase
Alanine aminotransferase (ALT/SGPT)
Aspartate aminotransferase (AST/SGOT)
Calcium
Chloride
Creatinine
Globulin (calculated)
Glucose
Inorganic phosphorus
Potassium
Sodium
Total bile acids
Total protein
Urea nitrogen (BUN)

Activated partial thromboplastin time was measured for all rats from blood samples collected from the vena cava at scheduled necropsy in Weeks 14 or 27. Pretest values were obtained in 5 rats/sex during the pretest/quarantine period.

Blood samples were also collected from the vena cava at scheduled necropsy (Week 14 or 27) to provide approximately 1 ml of plasma for the measurement of drug levels. These samples were collected after blood collection for measurement of activated partial thromboplastin times. The plasma samples were sent to Dr. Emil Lin as specified by the Sponsor. The results of the plasma drug level analysis are not included in this study report.

All animals which died on test were necropsied on that day. Ten animals/sex/dose were killed and necropsied in random order over a two consecutive day period (Days 91 and 92), except for five scheduled high dose males which either were found dead, or failed to recover from CO_2 anesthesia. The remaining recovery animals, except for one high dose female which failed to recover from CO_2 anesthesia (Week 16), were killed and necropsied in random order at the onset of Week 27, after a thirteen week recovery period. Euthanasia was accomplished by carbon dioxide asphyxiation, and an extensive necropsy was performed under the direction and supervision of the pathologist. Terminal body weights were collected prior to routine sacrifice.

The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin (NBF).

*Adrenal glands	Pancreas
Animal identification	Pituitary
*Brain	Prostate
Cecum	Rib with costochondral junction
Colon	Salivary gland (submaxillary)
Diaphragm	Sciatic nerve
Duodenum	Skeletal muscle
Esophagus	Skin with mammary gland
Eyes with harderian glands	Spinal cord (thoracic)
Femoral marrow smear	*Spleen
Gross lesions	Sternum with marrow
*Heart	Stomach
Ileum	*Testes with epididymides
Jejunum	Thymus
*Kidneys	Thyroid gland/Parathyroids
*Liver	Tongue
Lungs/Bronchi	Trachea
Lymph node (mesenteric)	Urinary bladder
*Ovaries	Uterus

*Weighed at scheduled necropsy. Paired organs were weighed as a unit.

All tissues and organs collected at necropsy were examined microscopically for all high dose (including the five high dose males which died on study) and control animals sacrificed after 13 weeks of treatment. If treatment-related lesions were observed at the high dose, those tissues/organs were examined microscopically for mid and low dose animals sacrificed in Week 14, and for control and high dose (and low and mid dose if necessary) recovery animals.

The myeloid:erythroid (M:E) ratio was determined from a femoral bone marrow smear collected from control and high dose animals at the Week 14 necropsy. Because treatment-related changes were not seen, M:E ratios were not determined from mid and low dose animals at Week 14, nor from the recovery animals (although bone marrow smears were collected from these animals).

3.4 Statistical Analyses

For each sex, Analysis of Variance tests was conducted on body weight, food consumption, hematology, clinical chemistry and organ weight data. Organ weight

analysis considered absolute weights and weights relative to body weight. Organ weight assessment generally consisted of comparison of organ weight/body weight ratios (% body weight), although brain and testis weight comparisons were usually considered on the basis of absolute values. If significant body weight loss occurs, organ weight/body weight ratios are often artificially elevated.

If a significant F ratio was obtained from an ANOVA test ($p \leq 0.05$), Dunnett's t test was used for pair-wise comparisons with the control group. The level of significance was $p \leq 0.05$. All summary and individual data are expressed on the basis of mg base/kg/day.

4. RESULTS

4.1 Dosage Formulations Analyses

The Analytical Chemistry Report is contained in Appendix 1. Dosage formulation analyses are shown in Table 2.

All dosing suspensions tested were within 10% of their target concentration.

4.2 Mortality and Clinical Signs/Observations

Summaries of clinical signs and clinical observations are presented in Tables 3 (males) and 4 (females). Individual clinical signs, daily incidence of clinical signs and summaries of weekly clinical observations are contained in Appendix 3.

Possible treatment-related deaths included five high dose males; four animals which were either found dead or failed to recover after CO_2 anesthesia for blood collection in Week 2; and one animal which died during Week 8. In addition, one high dose female died during the recovery period after failure to recover from CO_2 anesthesia for blood collection. No treatment-related daily clinical signs (1 - 2 hrs post dosing) were observed, however weekly clinical observations (physical examinations) included rough coat in almost all of the high dose animals, and in the majority of the males (sporadically) and a few females (infrequently) in the mid dose treatment groups. Hunched posture and emaciation was noted in one high dose male and dyspnea was seen in two high dose males which later died on the study. Blue ears, possible cyanosis, was observed in one high dose female. Also, one high dose female was observed to be emaciated in Week 13. No clinical signs of toxicity were observed in low dose or vehicle-treated animals during the treatment period. During the recovery period, no clinical signs of toxicity were observed, except for an infrequent rough coat.

- 2 M, 1F accidental

4.3 Body Weight

Summary of body weights and summary of weight gains for males are in Tables 5 and 6, respectively. The corresponding summaries for females are in Tables 7 and 8, respectively. Individual body weights and weight gains are contained in Appendix 4. In addition, summaries of body weights are graphically depicted in Figures 1 (males) and 2 (females).

During the treatment period, decreased body weight gains were apparent for high dose animals, resulting in significantly decreased body weights in these groups compared to controls. Decreased body weight gains were also observed in mid dose male rats and once in mid dose female rats (Week 11). This resulted in a decreased body weight in mid dose males (beginning Week 4) and in mid dose females (beginning Week 11) as compared to controls. During the recovery period, body weight gains of high and mid dose males were comparable to or significantly exceeded those of the controls. However, even with this accelerated weight gain the body weights remained significantly less than control animals up to the beginning of Weeks 16 (mid dose) and 24 (high dose). Furthermore, the body weights of the high but not mid dose males remained slightly depressed at the end of recovery period as compared to control animals. During the beginning of the recovery period, high dose females gained weight at a slightly higher rate than their respective controls. Their body weights remained significantly less than controls for the first third of the recovery period, and never fully recovered, similar to high dose males.

4.4 Food Consumption

Summaries of food consumption are in Tables 9 and 10 for males and females, respectively. Individual food consumption data are shown in Appendix 5.

Significantly reduced food consumption was apparent early in the treatment period for high (Week 1) and mid (Week 3) dose males. In high dose females, a significant decreased food intake was noted beginning in Week 2. Only once in mid dose females was decreased food consumption seen. Food consumption was not affected in low dose animals or during the recovery period in mid and high dose animals.

4.5 Clinical Pathology

Summaries of clinical chemistry tests for males and females are in Tables 11 and 12, respectively. Individual clinical chemistry data are in Appendix 6. Summaries of hematological tests for males and females are in Tables 13 and 14, respectively. Individual hematology data are in Appendix 7.

A slight increase in serum ALT was seen in high dose (Week 13) males (Table 11.1). This was also seen in mid but not high dose males in Week 8, and was therefore considered spurious. Significant increases in serum AST (from Week 2) were seen for

high dose animals until the end of the treatment period (Tables 11.2 and 12.2). Serum AST was also increased in Week 8 and possibly in Week 13 in mid dose males. By Week 16 (the first sampling time in the recovery period), AST values had returned to control levels. An increase in globulin levels in high dose males resulted in a corresponding decrease in A/G ratio in Week 2 (Tables 11.5 and 11.6). A decrease in serum albumin in high dose females in Week 2 (Table 12.4) and an increase in globulin levels in high dose females in Week 4 (Table 12.5) also resulted in decreases in A/G ratio observed in high dose females in Weeks 2 and 4 (Table 12.6). In high dose males, a slight, but significant elevation in total protein levels was seen in Week 2 (Table 11.3). Lactate dehydrogenase levels were also elevated in high dose males in Weeks 2 and 4, and in high dose females in Week 2 (Tables 11.9 and 12.9). These changes suggest WR238605 induced mild hepatotoxicity.

Significant anemia, as indicated by decreased RBC count, hematocrit, hemoglobin, and/or MCHC, was apparent at the high dose level and to a lesser extent in mid dose animals (Tables 13.1, 13.2, 13.3, 13.6, 14.1, 14.2, 14.3, and 14.6). A decrease in MCH was also seen in high dose males (Table 13.5). This anemia was present from Week 2 in the high dose animals, but generally was not seen in mid dose animals until Week 4. At the high dose level, the RBCs were polychromatic and in high dose females they were anisocytotic (irregularities in size). Reticulocytosis and/or the presence of Howell-Jolly bodies (immature RBCs with nuclear remnants), but not increased NRBCs, were seen as compensatory responses to the mild anemia in high dose animals and to a much lesser extent in mid dose animals (Tables 13.7, 13.8, 14.7 and 14.8). The induction of RBCs with Heinz bodies was also seen at the two highest dose levels, suggesting an oxidant nature of WR238605 (Tables 13.9 and 14.9). Methemoglobinemia was evident in high dose animals from Week 2 through Week 16 (the first sampling of the recovery period) and in mid dose animals from Week 4 to Week 13 (Tables 13.10 and 14.10). Reversal of anemia and methemoglobinemia was generally apparent by Week 21 for both sexes.

Leukocytosis was observed in high dose animals throughout the treatment period and in mid dose animals from Week 4 to the end of treatment (Tables 13.13 and 14.13). This generalized leukocytosis consisted of increased mature neutrophils, lymphocytes and/or monocytes (Tables 13.14, 13.16, 13.17, 14.14, 14.16, and 14.17). An increase in eosinophils was seen in Week 4 in mid dose males also (Table 13.18). A possible increase in WBCs was also seen in low dose females. A complete reversal of these effects on WBC count was apparent by Week 16 for mid dose males, by Week 13 for mid dose females, and by Week 21 for high dose animals.

A decrease in activated partial thromoplastin time was seen in high and possibly mid dose females but not males at the end of the dosing period, and was no longer observed at the end of the recovery period.

No other clinical pathology changes appeared to be related to WR238605 treatment. Increases and decreases were seen which were not considered biologically significant.

4.6 Ophthalmology Examinations

The Ophthalmology Report is contained in Appendix 8. WR238605 did not result in treatment-related ophthalmic lesions.

4.7 Organ Weights

Organ weight summaries for % body weight and for absolute values for males are in Tables 15 and 16, respectively. Corresponding summaries for females are in Tables 17 and 18. Individual organ weight data are contained in Appendix 9.

Absolute splenic weights in mid and high dose animals were significantly different from control animals (Tables 16 and 18). This splenomegaly was still apparent in high but not mid dose animals at the end of the recovery period. An increased relative kidney weight in high dose females but not males persisted throughout the recovery period. As such, increased relative kidney weights in mid and high dose animals may be treatment-related. Relative increases in the remaining organ weights in mid and high dose animals were considered to be related to their significantly decreased body weight gains.

4.8 Pathology

The Pathology Report is contained in Appendix 10. A summary of microscopic lesions is shown in Table 19.

The oral administration of WR238605 in rats was associated with changes in the lungs, kidneys, bone marrow, and spleen. Five possible treatment-related deaths occurred during the treatment period; four high dose males in Week 2 and one high dose male in Week 8. The cause of death of the four high dose males which died in Week 2 could not be determined. The cause of death of the high dose male which died in Week 8 was attributed to test-article related changes including alveolar proteinosis, hemoglobin nephrosis, and renal hemosiderosis. The aforementioned changes were also seen at the end of the dosing period as discussed below.

Alveolar proteinosis was observed in mid and high dose animals at the end of the treatment period. This was characterized by pale eosinophilic amphorous to fibrillar material in the alveoli and large discrete cells having abundant vacuolated cytoplasm in the alveolar and terminal bronchiolar lumen. This lesion was considered to be a direct test article-related change. Although alveolar proteinosis had been completely resolved by end of the recovery period, this resolution was associated with the development of chronic inflammation and hemosiderin deposition in alveolar macrophages during the recovery period. Chronic inflammation was seen as a focal or subcapsular change consisting of interstitial fibrosis, mononuclear cell infiltration, and sometimes hyperplasia of the alveolar or bronchiolar epithelium. These changes were only seen at the end of the recovery period.

Hemoglobin nephrosis and hemosiderin deposition in the kidney were seen in mid and high dose animals at the end of the dosing period. The nephrosis was characterized by proteinic droplets in the lumen of renal tubules and degenerative changes in tubular epithelium (irregular cell borders, proteinic cytoplasmic droplets, cytoplasmic vacuolation, and necrosis). Hemosiderin deposition was identified as variably-sized golden-brown granules in the cytoplasm of tubular epithelial cells. These changes were interpreted as consistent with the pathophysiologic response to a mild hemolytic anemia and its resolution following cessation of test article administration.

Hemosiderin deposition in the bone marrow was seen in high dose animals at the end of the dosing period. These findings are consistent with observations of hemolytic anemia seen in the kidney and thus was interpreted as a secondary effect of the erythrocyte destruction produced by drug treatment. Evaluation of the bone marrow smears revealed that WR238605 treatment did not produce any aberrations in M:E ratios. The bone marrow changes was reversible by the end of the recovery period.

Splenic hyperplasia, consisting of an increase in normal cellular components, was observed in mid and high dose males, and high dose females at the end of the dosing period. This hyperplasia was no longer evident at the end of the recovery period.

No other microscopic changes were considered to be related to WR238605 treatment.

5. DISCUSSION/CONCLUSION

This study evaluated the toxicity of WR238605 in CD® rats following thirteen weeks of daily oral (gavage) administration. A thirteen week recovery period was included for all groups. The results are summarized in Table 1. Five possible treatment-related deaths occurred among high dose males in the dosing period; four animals in Week 2 (undetermined causes of death) and one animal in Week 8 (treatment-related changes observed). Body weight gains and food consumption were decreased in mid and high dose rats during the treatment period, with recovery seen thereafter. These significant decreases in body weight gains appeared to account for the apparent increase in the relative weight of most of the organs harvested in mid and high dose animals. Treatment-related ophthalmic lesions were not observed.

Treatment-related anemia was observed for animals at the high (beginning in Week 2) and mid (beginning in Week 4) dose levels. The anemic state consisted of a significant decrease in RBCs, hemoglobin, hematocrit, and MCHC. In the high dose, RBCs were polychromatic and anisocytotic (females). Compensatory physiologic responses included reticulocytosis, splenanomegaly, induction of Heinz bodies, and presence of Howell-Jolly bodies. The anemia was accompanied by several histologic changes including splenic hyperplasia, renal and bone marrow hemosiderosis, and hemoglobin nephropathy. These "lesions" were apparently secondary to the anemia, which was considered hemolytic in origin. The anemic state and the accompanying secondary lesions were generally reversible after cessation of treatment, except for renal hemosiderosis which was still in the process of resolution as judged by a decrease in severity and occurrence, and splenanomegaly which was still seen in high dose animals.

Alveolar proteinosis was observed in all mid and high dose animals sacrificed at the end of the dosing period. Furthermore, alveolar proteinosis, as well as, hemoglobin nephrosis and renal hemosiderosis, may have been contributing factors in the death of a high dose male in Week 8. Although alveolar proteinosis had resolved by the end of the recovery period, the process of resolution resulted in the development of chronic inflammation and hemosiderosis of the lung.

Increases in ALT, AST, LDH, and/or ALKP serum levels and decreases in A/G ratio were observed in high dose animals and possibly mid dose males, however histopathologic changes in the liver were not apparent. As noted above, hemoglobin nephropathy and hemosiderosis were noted at the high and mid dose. However, these changes were observed without significant corresponding alterations in clinical chemistry parameters. The above renal changes were considered secondary to the observed hemolytic anemia, as free hemoglobin was apparently deposited in the renal tubules.

Generalized leukocytosis was seen in high dose animals form Week 2 and mid dose animals from Week 4 until the end of the treatment period. These were still present in high dose animals by Week 16 (the first time of sampling in the recovery period), but were resolved by Week 21. The leukocytotic episode was possibly an indirect effect of the stress produced by the hemolytic anemic and/or methemoglobinemic state.

In summary, the primary toxic affects were seen in the RBCs, lungs, and liver. Significant methemoglobin production was observed in mid and high dose animals, but was reversible. Microscopic lesions in the spleen, kidney, and bone marrow were secondary to mild hemolytic anemia. Toxicity was limited to the two highest dose levels. Decreased food consumption, decreased body weight gains, methemoglobin production and mild anemia were observed at the mid and high dose levels, but were readily reversible after treatment cessation. Increases in serum ALT, AST, and/or LDH and decreased A/G ratio in high dose animals and possibly in mid dose males suggested mild hepatotoxicity, however histopathologic lesions were not seen. Leukocytosis possibly secondary to stress and consisting of increased number of lymphocytes, neutrophils, and/or monocytes was seen in the treatment period at the two highest dose levels and was reversible after cessation of treatment. Because the aforementioned toxic responses were limited to mid and high dose animals, a no-adverse effect level of WR238605 was judged to be 0.5 mg base/kg/day.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	E. Marianna Furedi-Machacek, D.V.M.
Pathologist	Michael J. Tomlinson, D.V.M., Ph.D., D.A.C.V.P.
Analytical Chemist	Ian R. Tebbett, Ph.D.
Clinical Veterinarian	James E. Artwohl, D.V.M., Ph.D., D.A.C.L.A.M.
Ophthalmologist	Samuel J. Vainisi, D.V.M., D.A.C.V.O.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Clinical Pathology	Maria Lang, A.T., C.V.T.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

Report preparation was assisted by Drs. E. Marianna Furedi-Machacek and Clyde W. Wheeler.

7. ARCHIVES

The raw data, specimens, test article reserves, and final report are archived at the Toxicology Research Laboratory (TRL), University of Illinois at Chicago (UIC), Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

Table 1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

Summary of Toxic Responses

Dose (mg base/kg/day)	0	0.5	6.0	18.0
Rats/Sex	10 + 10[a]	10 + 10[a]	10 + 10[a]	10 + 10[a]
Deaths	-	NE	NE	5(M) + 1(F?)
Body Weight Gain	-	NE	↓	↓
Food Consumption	-	NE	↓ (M) (F?)	↓
Clinical Observations	-	NE	Rough coat	Rough coat Hunched posture (1M) Blue ears (1F) Dyspnea (2M) Emaciation (1M + 1F)
Hematology[b]	-	NE	↑ METHGB ↓ RBC (F) (M?) ↓ HCT (M) ↓ HGB ↓ MCHC (M) ↑ HEINZ (M) ↑ RETIC ↑ LEUK ↑ MNEUT ↑ LYMPH (M) (F?) ↑ MONO (M)	↑ METHGB ↓ RBC ↓ HGB ↓ HCT ↓ MCH (M) ↓ MCHC ↑ HEINZ ↑ RETIC ↑ LEUK ↑ MNEUT ↑ LYMPH ↑ MONO ↓APTT (F)
Clinical Chemistry[c]	-	NE	↑ AST (M)	↑ ALT (M?) ↑ AST ↑ TP (M) ↓ ALB (F) ↑ GLOB ↓ A/G ↑ LDH
Ophthalmology	-	NE	NE	NE
Organ Weights	-	NE	↑ Kidneys (?) ↑ Spleen	↑ Kidneys (?) ↑ Spleen
Histopathology	-	NE	Lungs - alveolar proteinosis Kidney - hemoglobin nephrosis hemosiderin pigment Spleen - hyperplasia (M)	Lungs - alveolar proteinosis Kidneys - hemoglobin nephrosis hemosiderin pigment Bone Marrow - hemosiderin pigment Spleen - hyperplasia
Recovery Period	Essentially complete recovery occurred by the end of the 3 month recovery period. The exceptions, generally secondary response, were incomplete resolution of hemosiderosis of the kidney and splenomegly in high dose animals. In addition, as part of the resolution of alveolar proteinosis, chronic inflammation and hemosiderosis developed in the lungs. Relative kidney weight was also increased in high dose females.			
CONCLUSIONS	The primary toxic affects were seen in the RBCs, lungs, and liver. Significant methemoglobin production was observed in mid and high dose animals, but was reversible. Microscopic lesions in the spleen, kidney, and bone marrow of mid and high dose animals were secondary to mild hemolytic anemia. Toxicity was limited to the two highest dose levels. Decreased food consumption, decreased body weight gains, methemoglobin production and mild anemia were observed at the mid and high dose levels, but were readily reversible after treatment cessation. Increases in serum ALT, AST, and/or LDH and decreased A/G ratio in high dose animals and possibly mid dose males suggested mild hepatotoxicity, however histopathologic lesions were not seen. Leukocytosis, possibly a secodary response to stress, consisting of increased lymphocytes, ueutrophils, and/or monocytes was seen in the treatment period at the highest dose levels and was reversible after cessation of treatment. Because toxic responses were limited to mid and high dose animals, a no-effect dose level of WR238605 was seen at 0.5 mg/kg/day.			

[a]Recovery animals.

[b]METHGB = methemoglobin, RBC = red blood cells, HCT = hematocrit, HGB = hemoglobin, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, HEINZ = Heinz bodies, RETIC = reticulocytes, LEUK = leukocytes, MNEUT = mature neutrophils, LYMPH = lymphocytes, MONO = monocytes, EOSIN = eosinophils, APTT = activated partial thromboplastin time

[c]AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALB = albumin, GLOB = globulin, A/G = A/G ratio, LDH = lactate dehydrogenase, BUN = blood urea nitrogen, CREA = creatinine.

? = Possible or marginal effect

NE = No effect

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

Table 2

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

Dosage Formulations Analyses[a]

Target Concentration (mg base/ml)	Weeks 1 & 2	% Target	Weeks 7 & 8	% Target	Week 13	% Target
0	0.00	----	0.00	----	----	----
0.1	0.098 ± 0.007	98.0	0.104 ± 0.0002	104.0	0.099 ± 0.001	99.0
1.2	1.167 ± 0.040	97.2	1.205 ± 0.005	100.4	1.179 ± 0.002	98.2
3.6	3.694 ± 0.045	102.6	3.643 ± 0.008	101.2	3.482 ± 0.0004	96.7

[a]Mean ± standard deviation for triplicate runs.

Table 3

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 098

SEX: MALE

DOSE:(mg/kg)	0	0.5	6.0	18.0
GROUP:	1M	2M	3M	4M
TREATMENT PERIOD				
Accidental Death	0	0	0	2
Scheduled Sacrifice	10	10	10	5
Animal Found Dead	0	0	0	3
Emaciated	0	0	0	1
Rough Coat	0	0	14	18
Dyspnea	0	0	0	2
Hunched Posture	0	0	0	1
Total Number of Animals	20	20	20	20
RECOVERY PERIOD				
Scheduled Sacrifice	10	10	10	10
Rough Coat	0	1	1	6
Total Number of Animals	10	10	10	10

Tx + Recovery animals

Recovery animals

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 098 SEX: FEMALE

DOSE:(mg/kg)	0	0.5	6.0	18.0
GROUP:	1F	2F	3F	4F

TREATMENT PERIOD

Scheduled Sacrifice	10	10	10	10
Emaciated	0	0	0	1
Rough Coat	0	0	3	20
Blue Ears	0	0	0	1
Total Number of Animals	20	20	20	20

RECOVERY PERIOD

Accidental Death	0	0	0	1
Scheduled Sacrifice	10	10	10	9
Rough Coat	0	0	0	6
Total Number of Animals	10	10	10	10

Table 5

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 098 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1M	0.5 2M	6.0 3M	18.0 4M
TREATMENT PERIOD					
DAY -7	MEAN	168.3	169.0	169.1	168.5
	S.D.	12.91	13.06	12.78	12.38
	N	20	20	20	20
DAY 0	MEAN	230.1	228.6	227.0	228.2
	S.D.	15.66	14.38	14.43	15.44
	N	20	20	20	20
DAY 7	MEAN	282.3	276.5	277.1	256.4**
	S.D.	18.67	24.08	19.08	18.48
	N	20	20	20	20
DAY 14	MEAN	317.2	312.6	311.3	269.5**
	S.D.	22.87	29.23	21.37	21.40
	N	20	20	20	16
DAY 21	MEAN	353.4	349.5	333.6*	288.6**
	S.D.	24.16	26.29	23.94	25.33
	N	20	20	20	16
DAY 28	MEAN	379.3	375.8	348.8**	297.4**
	S.D.	25.58	27.68	24.38	26.33
	N	20	20	20	16
DAY 35	MEAN	410.3	403.5	368.6**	309.7**
	S.D.	29.72	29.14	28.41	40.57
	N	20	20	20	16
DAY 42	MEAN	435.0	430.1	389.4**	335.2**
	S.D.	33.39	32.34	30.11	37.88
	N	20	20	20	16
DAY 49	MEAN	457.1	451.4	399.1**	354.5**
	S.D.	35.58	33.19	32.52	30.58
	N	20	20	20	16
DAY 56	MEAN	468.9	463.2	408.4**	360.8**
	S.D.	37.93	34.96	35.77	29.24
	N	20	20	20	15
DAY 63	MEAN	483.8	480.9	421.6**	371.7**
	S.D.	41.01	36.19	37.95	24.75
	N	20	20	20	15
DAY 70	MEAN	499.1	496.4	433.7**	382.3**
	S.D.	42.44	36.97	38.19	25.47
	N	20	20	20	15
DAY 77	MEAN	513.0	510.0	444.2**	385.3**
	S.D.	44.05	39.93	39.02	28.10
	N	20	20	20	15
DAY 84	MEAN	526.2	518.2	447.8**	391.3**
	S.D.	46.82	43.49	43.25	31.13
	N	20	20	20	15
DAY 88	MEAN	532.1	526.5	452.5**	394.7**
	S.D.	47.30	43.25	41.29	28.76
	N	20	20	20	15
DAY 91	MEAN	521.9	511.3	445.7**	382.3**
	S.D.	52.44	37.07	48.79	27.09
	N	10	10	10	10

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

THIRTEEN WEEK ORAL TOXICITY STUDY OF
WR 238605 WITH A THIRTEEN WEEK RECOVERY
PERIOD IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 098 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1M	0.5 2M	6.0 3M	18.0 4M
RECOVERY PERIOD					
DAY 98	MEAN	537.9	528.5	475.1**	417.2**
	S.D.	55.13	37.78	50.28	24.31
	N	10	10	10	10
DAY 105	MEAN	555.8	545.4	495.9*	435.5**
	S.D.	58.02	41.54	51.22	26.65
	N	10	10	10	10
DAY 112	MEAN	554.4	546.9	502.3	442.2**
	S.D.	63.52	45.81	51.97	25.39
	N	10	10	10	10
DAY 119	MEAN	569.7	559.1	519.4	469.1**
	S.D.	63.28	45.14	50.85	26.94
	N	10	10	10	10
DAY 126	MEAN	581.5	571.9	546.3	492.2**
	S.D.	62.61	44.66	60.79	27.99
	N	10	10	10	10
DAY 133	MEAN	591.3	583.0	560.2	503.1**
	S.D.	65.21	44.09	62.90	31.01
	N	10	10	10	10
DAY 140	MEAN	585.9	580.7	563.4	508.8**
	S.D.	72.10	47.71	58.73	31.27
	N	10	10	10	10
DAY 147	MEAN	601.9	593.1	576.6	525.7*
	S.D.	67.28	48.68	60.92	40.04
	N	10	10	10	10
DAY 154	MEAN	614.3	603.8	590.1	544.5*
	S.D.	70.34	51.14	61.02	39.20
	N	10	10	10	10
DAY 161	MEAN	622.5	614.6	603.4	559.2
	S.D.	68.38	51.58	59.93	37.85
	N	10	10	10	10
DAY 168	MEAN	632.3	617.9	614.8	572.9
	S.D.	70.91	52.52	64.28	42.22
	N	10	10	10	10
DAY 175	MEAN	635.1	623.3	621.7	580.1
	S.D.	71.76	54.87	63.46	44.09
	N	10	10	10	10
DAY 179	MEAN	642.3	626.8	627.1	585.7
	S.D.	68.58	52.02	65.33	44.08
	N	10	10	10	10

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 6

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 098 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1M	0.5 2M	6.0 3M	18.0 4M
TREATMENT PERIOD					
DAY 7	MEAN	52.2	47.9	50.1	28.2**
	S.D.	5.86	14.41	8.79	9.21
	N	20	20	20	20
DAY 14	MEAN	34.9	36.1	34.2	11.2**
	S.D.	9.01	8.95	8.07	13.17
	N	20	20	20	16
DAY 21	MEAN	36.2	36.9	22.3**	19.1**
	S.D.	5.13	8.11	6.57	12.66
	N	20	20	20	16
DAY 28	MEAN	25.9	26.3	15.2**	8.8**
	S.D.	8.70	7.57	6.04	8.27
	N	20	20	20	16
DAY 35	MEAN	31.0	27.6	19.8*	12.3**
	S.D.	9.49	4.37	8.02	22.06
	N	20	20	20	16
DAY 42	MEAN	24.7	26.6	20.8	25.5
	S.D.	6.90	5.66	7.90	11.88
	N	20	20	20	16
DAY 49	MEAN	22.0	21.4	9.7**	19.3
	S.D.	5.54	4.46	6.20	14.49
	N	20	20	20	16
DAY 56	MEAN	11.8	11.7	9.4	2.4**
	S.D.	7.35	7.00	9.07	10.31
	N	20	20	20	15
DAY 63	MEAN	14.9	17.8	13.2	10.9
	S.D.	6.39	5.63	8.66	13.22
	N	20	20	20	15
DAY 70	MEAN	15.4	15.5	12.1	10.6
	S.D.	4.58	5.32	4.83	9.30
	N	20	20	20	15
DAY 77	MEAN	13.8	13.6	10.5	3.0**
	S.D.	5.48	5.16	4.80	10.00
	N	20	20	20	15
DAY 84	MEAN	13.2	8.2	3.7**	6.0*
	S.D.	5.81	7.47	8.29	11.15
	N	20	20	20	15
DAY 88	MEAN	5.9	8.3	4.7	3.4
	S.D.	5.30	3.76	8.00	10.76
	N	20	20	20	15
TOTAL GAIN	MEAN	302.0	297.9	225.5**	166.0**
	S.D.	44.57	34.94	35.52	25.31
	N	20	20	20	15

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 098 SEX: MALE

PERIOD	DOSE: (mg/kg) / GROUP:	0 / 1M	0.5 / 2M	6.0 / 3M	18.0 / 4M
RECOVERY PERIOD					
DAY 98	MEAN	16.0	17.3	29.4**	35.0**
	S.D.	5.79	7.42	9.74	7.20
	N	10	10	10	10
DAY 105	MEAN	17.9	16.9	20.8	18.3
	S.D.	5.20	4.43	6.14	7.59
	N	10	10	10	10
DAY 112	MEAN	-1.4	1.4	6.4	6.7
	S.D.	9.21	7.75	6.49	7.09
	N	10	10	10	10
DAY 119	MEAN	15.2	12.2	17.1	26.9**
	S.D.	5.58	5.44	9.40	6.99
	N	10	10	10	10
DAY 126	MEAN	11.9	12.9	26.9**	23.1*
	S.D.	6.20	7.94	15.59	5.78
	N	10	10	10	10
DAY 133	MEAN	9.7	11.1	13.9	10.9
	S.D.	7.21	5.94	7.51	5.83
	N	10	10	10	10
DAY 140	MEAN	-5.4	-2.3	3.2*	5.6**
	S.D.	9.72	7.34	6.00	4.15
	N	10	10	10	10
DAY 147	MEAN	16.0	12.4	13.2	16.9
	S.D.	6.88	7.23	8.05	13.75
	N	10	10	10	10
DAY 154	MEAN	12.4	10.7	13.5	18.9
	S.D.	5.73	5.72	3.28	8.72
	N	10	10	10	10
DAY 161	MEAN	8.2	10.8	13.2	14.7
	S.D.	9.90	4.12	5.75	6.54
	N	10	10	10	10
DAY 168	MEAN	9.8	3.3	11.5	13.7
	S.D.	8.35	5.19	6.18	7.05
	N	10	10	10	10
DAY 175	MEAN	2.8	5.4	6.9	7.2
	S.D.	3.53	6.06	5.78	5.51
	N	10	10	10	10
DAY 179	MEAN	7.2	3.5	5.3	5.6
	S.D.	5.66	4.85	5.47	3.12
	N	10	10	10	10
TOTAL GAIN	MEAN	120.4	115.5	181.4**	203.5**
	S.D.	21.28	22.82	31.16	42.46
	N	10	10	10	10

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 7

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 098 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1F	0.5 2F	6.0 3F	18.0 4F
TREATMENT PERIOD					
DAY -7	MEAN	137.9	138.1	137.9	137.5
	S.D.	9.37	9.22	9.44	9.50
	N	20	20	20	20
DAY 0	MEAN	168.7	168.2	164.2	166.1
	S.D.	11.40	10.84	9.31	9.20
	N	20	20	20	20
DAY 7	MEAN	191.1	189.5	187.6	181.1*
	S.D.	12.31	13.07	10.87	9.46
	N	20	20	20	20
DAY 14	MEAN	206.3	203.7	203.8	186.5**
	S.D.	12.28	13.47	10.04	12.13
	N	20	20	20	20
DAY 21	MEAN	220.1	218.6	216.9	196.6**
	S.D.	11.21	14.18	11.16	11.75
	N	20	20	20	20
DAY 28	MEAN	228.0	229.3	223.4	203.1**
	S.D.	12.25	17.11	10.66	12.13
	N	20	20	20	20
DAY 35	MEAN	240.8	240.9	233.3	219.8**
	S.D.	15.29	17.49	12.86	13.25
	N	20	20	20	20
DAY 42	MEAN	253.3	249.2	243.3	226.8**
	S.D.	16.28	20.16	12.65	14.16
	N	20	20	20	20
DAY 49	MEAN	260.1	255.1	248.7	234.8**
	S.D.	16.72	20.45	11.40	14.62
	N	20	20	20	20
DAY 56	MEAN	260.1	255.1	248.4	227.8**
	S.D.	18.15	20.44	10.59	17.04
	N	20	20	20	20
DAY 63	MEAN	267.9	265.5	256.8	238.1**
	S.D.	20.05	21.98	12.61	14.20
	N	20	20	20	20
DAY 70	MEAN	275.7	269.8	260.7*	241.6**
	S.D.	19.37	21.47	12.83	13.33
	N	20	20	20	20
DAY 77	MEAN	279.7	278.2	264.1*	245.1**
	S.D.	19.66	20.83	14.24	13.78
	N	20	20	20	20
DAY 84	MEAN	286.1	278.5	267.6**	245.7**
	S.D.	21.22	23.17	12.37	15.72
	N	20	20	20	20
DAY 88	MEAN	288.9	283.6	271.2*	249.6**
	S.D.	20.56	22.35	13.29	18.39
	N	20	20	20	20
DAY 91	MEAN	288.5	276.6	271.1	236.9**
	S.D.	22.38	25.11	11.39	14.37
	N	10	10	10	10

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

THIRTEEN WEEK ORAL TOXICITY STUDY OF
WR 238605 WITH A THIRTEEN WEEK RECOVERY
PERIOD IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 098 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1F	0.5 2F	6.0 3F	18.0 4F
RECOVERY PERIOD					
DAY 98	MEAN	294.1	285.4	284.6	264.1**
	S.D.	20.79	25.94	10.91	14.83
	N	10	10	10	10
DAY 105	MEAN	299.3	291.7	291.4	268.0**
	S.D.	19.40	26.17	14.52	15.58
	N	10	10	10	10
DAY 112	MEAN	293.3	285.4	285.7	264.1**
	S.D.	19.43	28.64	13.91	15.78
	N	10	10	10	9
DAY 119	MEAN	307.2	299.6	295.9	277.3*
	S.D.	18.60	30.78	16.19	16.19
	N	10	10	10	9
DAY 126	MEAN	310.4	303.9	300.5	286.0
	S.D.	22.67	33.16	18.75	15.24
	N	10	10	10	9
DAY 133	MEAN	314.8	308.7	306.4	289.0
	S.D.	23.78	36.46	21.98	15.03
	N	10	10	10	9
DAY 140	MEAN	311.0	302.8	302.5	285.8
	S.D.	24.03	31.66	18.50	18.15
	N	10	10	10	9
DAY 147	MEAN	323.4	308.6	312.5	286.5*
	S.D.	29.87	29.61	18.56	25.03
	N	10	10	10	9
DAY 154	MEAN	329.9	314.7	315.0	301.6
	S.D.	32.80	30.53	24.08	18.00
	N	10	10	10	9
DAY 161	MEAN	332.0	320.1	322.1	303.2
	S.D.	32.36	34.81	17.89	18.60
	N	10	10	10	9
DAY 168	MEAN	331.2	322.6	322.1	307.0
	S.D.	31.14	35.95	20.87	19.41
	N	10	10	10	9
DAY 175	MEAN	334.3	329.2	317.3	307.8
	S.D.	31.89	38.88	23.34	19.22
	N	10	10	10	9
DAY 179	MEAN	335.6	332.1	323.2	313.1
	S.D.	33.11	38.60	19.41	21.45
	N	10	10	10	9

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 8

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 098 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1F	0.5 2F	6.0 3F	18.0 4F
TREATMENT PERIOD					
DAY 7	MEAN	22.4	21.3	23.4	15.0**
	S.D.	3.89	4.94	5.18	6.92
	N	20	20	20	20
DAY 14	MEAN	15.1	14.1	16.2	5.4**
	S.D.	5.34	4.60	5.33	8.77
	N	20	20	20	20
DAY 21	MEAN	13.8	14.9	13.1	10.1*
	S.D.	4.43	5.18	3.48	5.23
	N	20	20	20	20
DAY 28	MEAN	7.9	10.7	6.5	6.4
	S.D.	5.58	6.54	5.29	8.60
	N	20	20	20	20
DAY 35	MEAN	12.8	11.7	9.9	16.8
	S.D.	7.35	4.40	8.46	9.23
	N	20	20	20	20
DAY 42	MEAN	12.5	8.3	10.0	6.9*
	S.D.	7.57	5.89	5.96	5.35
	N	20	20	20	20
DAY 49	MEAN	6.8	5.9	5.4	8.0
	S.D.	7.63	4.88	4.78	5.20
	N	20	20	20	20
DAY 56	MEAN	0.0	0.0	-0.3	-7.0**
	S.D.	6.61	5.91	3.82	10.48
	N	20	20	20	20
DAY 63	MEAN	7.8	10.4	8.3	10.3
	S.D.	4.82	5.72	5.14	12.26
	N	20	20	20	20
DAY 70	MEAN	7.8	4.3	4.0*	3.5*
	S.D.	5.77	5.01	4.17	4.38
	N	20	20	20	20
DAY 77	MEAN	4.0	8.4*	3.3	3.5
	S.D.	6.39	3.68	5.26	4.17
	N	20	20	20	20
DAY 84	MEAN	6.4	0.2*	3.5	0.6*
	S.D.	7.69	5.70	5.45	9.27
	N	20	20	20	20
DAY 88	MEAN	2.8	5.2	3.7	3.9
	S.D.	6.10	3.93	4.31	7.16
	N	20	20	20	20
TOTAL GAIN	MEAN	120.2	115.4	107.0*	83.4**
	S.D.	13.86	18.39	11.48	14.99
	N	20	20	20	20

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

THIRTEEN WEEK ORAL TOXICITY STUDY OF
WR 238605 WITH A THIRTEEN WEEK RECOVERY
PERIOD IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 098 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1F	0.5 2F	6.0 3F	18.0 4F
RECOVERY PERIOD					
DAY 98	MEAN	5.7	8.8	13.6*	27.2**
	S.D.	8.52	4.05	6.26	7.55
	N	10	10	10	10
DAY 105	MEAN	5.2	6.3	6.7	3.9
	S.D.	8.31	4.46	7.20	7.23
	N	10	10	10	10
DAY 112	MEAN	-6.1	-6.3	-5.7	-5.1
	S.D.	7.09	7.09	3.99	5.28
	N	10	10	10	9
DAY 119	MEAN	13.9	14.3	10.2	13.2
	S.D.	8.74	6.67	5.37	5.39
	N	10	10	10	9
DAY 126	MEAN	3.2	4.3	4.6	8.7
	S.D.	10.28	5.47	6.23	4.04
	N	10	10	10	9
DAY 133	MEAN	4.5	4.8	5.9	3.0
	S.D.	6.41	7.54	6.22	6.43
	N	10	10	10	9
DAY 140	MEAN	-3.9	-5.9	-3.9	-3.2
	S.D.	5.56	9.17	6.58	7.33
	N	10	10	10	9
DAY 147	MEAN	12.4	5.9	10.0	0.6*
	S.D.	10.15	6.51	4.19	14.69
	N	10	10	10	9
DAY 154	MEAN	6.5	6.1	2.5	15.2
	S.D.	9.82	3.33	7.49	16.02
	N	10	10	10	9
DAY 161	MEAN	2.1	5.5	7.2	1.6
	S.D.	6.62	5.75	7.42	4.44
	N	10	10	10	9
DAY 168	MEAN	-0.8	2.4	0.0	3.8
	S.D.	6.83	6.53	6.56	6.05
	N	10	10	10	9
DAY 175	MEAN	3.1	6.7	-4.8*	0.8
	S.D.	7.58	6.26	7.21	4.78
	N	10	10	10	9
DAY 179	MEAN	1.3	2.9	5.9	5.3
	S.D.	5.08	4.29	5.58	3.15
	N	10	10	10	9
TOTAL GAIN	MEAN	47.1	55.5	52.1	75.7**
	S.D.	21.71	16.28	13.59	11.24
	N	10	10	10	9

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 9

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 098 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1M	0.5 2M	6.0 3M	18.0 4M
TREATMENT PERIOD					
DAY 0	INTAKE (g)	18.7	19.0	18.7	18.7
	S.D.	1.62	4.23	1.62	1.62
	N	20	20	20	20
DAY 7	INTAKE (g)	22.4	22.0	21.9	19.0**
	S.D.	1.63	2.37	2.08	1.68
	N	20	20	20	20
DAY 11	INTAKE (g)	24.7	25.1	25.1	16.4**
	S.D.	1.83	2.53	2.66	5.68
	N	20	19	20	19
DAY 21	INTAKE (g)	24.5	25.3	22.3*	18.1**
	S.D.	1.89	2.75	2.41	2.07
	N	20	20	20	16
DAY 25	INTAKE (g)	27.2	25.8	22.1**	19.4**
	S.D.	2.79	2.05	2.59	2.85
	N	20	19	20	16
DAY 35	INTAKE (g)	25.7	26.7	22.4**	18.5**
	S.D.	2.22	1.86	2.47	4.54
	N	20	20	20	16
DAY 42	INTAKE (g)	26.2	25.8	22.3**	20.0**
	S.D.	3.79	2.36	1.84	3.14
	N	20	20	20	16
DAY 49	INTAKE (g)	25.9	26.3	23.1**	21.7**
	S.D.	2.33	1.90	2.49	1.99
	N	20	20	20	16
DAY 53	INTAKE (g)	27.4	27.3	24.9*	23.3**
	S.D.	2.75	2.22	2.92	3.25
	N	20	20	20	16
DAY 63	INTAKE (g)	26.3	26.0	22.6**	21.1**
	S.D.	3.05	1.95	2.49	1.61
	N	20	20	20	15
DAY 70	INTAKE (g)	26.5	26.3	23.0**	20.3**
	S.D.	3.03	1.98	3.20	1.40
	N	20	20	20	15
DAY 77	INTAKE (g)	25.4	26.5	22.6**	19.9**
	S.D.	2.42	2.33	2.70	2.07
	N	20	20	20	15

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

THIRTEEN WEEK ORAL TOXICITY STUDY OF
WR 238605 WITH A THIRTEEN WEEK RECOVERY
PERIOD IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 098 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1M	0.5 2M	6.0 3M	18.0 4M
RECOVERY PERIOD					
DAY 98	INTAKE (g)	24.8	25.5	24.7	23.9
	S.D.	4.15	2.22	2.65	2.05
	N	10	10	10	10
DAY 105	INTAKE (g)	26.4	26.3	23.9	23.2
	S.D.	4.38	3.04	3.10	4.36
	N	10	10	10	9
DAY 109	INTAKE (g)	28.7	26.9	28.2	25.9
	S.D.	2.96	2.82	4.14	2.10
	N	9	10	10	10
DAY 119	INTAKE (g)	26.8	26.3	28.5	28.1
	S.D.	4.65	1.54	5.03	2.78
	N	10	10	10	10
DAY 126	INTAKE (g)	26.6	27.3	28.8	29.8
	S.D.	3.13	1.92	4.44	2.56
	N	10	10	10	10
DAY 133	INTAKE (g)	26.3	25.9	27.9	26.7
	S.D.	2.71	2.11	4.54	2.16
	N	10	10	10	10
DAY 137	INTAKE (g)	27.1	27.8	29.7	29.2
	S.D.	4.05	2.61	4.49	4.21
	N	10	10	10	10
DAY 147	INTAKE (g)	26.4	26.9	28.6	29.0
	S.D.	5.65	2.06	3.48	2.86
	N	10	10	10	10
DAY 154	INTAKE (g)	27.1	26.9	27.8	28.5
	S.D.	3.06	2.55	3.00	2.43
	N	10	10	10	10
DAY 161	INTAKE (g)	27.1	26.5	28.5	28.8
	S.D.	3.10	1.77	2.14	2.82
	N	10	10	10	10
DAY 168	INTAKE (g)	27.2	26.2	28.5	27.6
	S.D.	3.80	1.43	3.13	2.81
	N	10	10	10	10
DAY 175	INTAKE (g)	27.6	28.5	30.6	28.3
	S.D.	4.00	3.22	2.87	1.96
	N	10	10	10	10

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

Table 10

THIRTEEN WEEK ORAL TOXICITY STUDY OF
WR 238605 WITH A THIRTEEN WEEK RECOVERY
PERIOD IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 098 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1F	0.5 2F	6.0 3F	18.0 4F
TREATMENT PERIOD					
DAY 0	INTAKE (g)	14.4	13.9	13.8	14.1
	S.D.	1.67	1.18	1.71	1.26
	N	19	20	20	19
DAY 7	INTAKE (g)	17.3	16.7	17.2	15.6
	S.D.	2.59	1.17	2.69	1.63
	N	20	20	20	20
DAY 11	INTAKE (g)	19.4	20.5	20.1	15.1**
	S.D.	2.77	3.70	4.12	3.56
	N	20	20	20	20
DAY 21	INTAKE (g)	18.7	18.4	19.2	14.2**
	S.D.	2.21	1.88	3.00	1.41
	N	20	20	20	20
DAY 25	INTAKE (g)	22.5	21.3	20.0	16.7**
	S.D.	4.01	3.29	4.10	3.37
	N	19	20	20	20
DAY 35	INTAKE (g)	20.1	19.3	19.5	17.5**
	S.D.	2.04	1.63	3.24	2.79
	N	20	20	20	20
DAY 42	INTAKE (g)	20.5	19.1	19.6	16.2**
	S.D.	3.73	2.14	3.41	2.36
	N	20	20	20	20
DAY 49	INTAKE (g)	18.8	18.8	18.8	16.3**
	S.D.	1.50	2.56	1.56	1.56
	N	20	20	20	20
DAY 53	INTAKE (g)	21.6	20.0	19.8	19.2**
	S.D.	2.74	2.24	2.42	2.50
	N	20	20	20	20
DAY 63	INTAKE (g)	19.3	18.8	18.4	16.6**
	S.D.	1.84	2.17	2.30	2.05
	N	20	20	20	20
DAY 70	INTAKE (g)	19.7	19.0	17.6**	15.0**
	S.D.	2.91	2.20	1.56	1.41
	N	20	20	20	20
DAY 77	INTAKE (g)	18.6	18.0	18.2	14.8**
	S.D.	2.14	1.88	2.63	1.14
	N	20	20	20	20

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF
WR 238605 WITH A THIRTEEN WEEK RECOVERY
PERIOD IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 098 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1F	0.5 2F	6.0 3F	18.0 4F
RECOVERY PERIOD					
DAY 98	INTAKE (g)	19.4	16.8	19.0	18.1
	S.D.	3.50	2.04	1.33	1.38
	N	9	9	10	9
DAY 105	INTAKE (g)	18.4	16.2	19.3	16.5
	S.D.	2.14	1.75	1.91	2.43
	N	10	10	10	10
DAY 109	INTAKE (g)	20.3	17.5*	20.5	20.0
	S.D.	2.93	2.14	1.98	1.87
	N	9	10	10	10
DAY 119	INTAKE (g)	19.7	18.1	20.5	20.6
	S.D.	2.68	2.76	1.96	2.36
	N	10	10	10	9
DAY 126	INTAKE (g)	20.2	18.1	20.7	22.2
	S.D.	3.38	2.28	3.56	3.16
	N	10	10	10	9
DAY 133	INTAKE (g)	19.7	16.6	20.3	20.2
	S.D.	3.19	2.57	3.69	4.97
	N	10	10	10	9
DAY 137	INTAKE (g)	19.7	18.8	19.4	20.3
	S.D.	2.57	3.95	1.62	3.80
	N	10	10	10	9
DAY 147	INTAKE (g)	20.4	17.8	19.8	19.3
	S.D.	2.75	1.78	1.54	3.40
	N	10	10	10	9
DAY 154	INTAKE (g)	19.8	17.8	18.9	20.3
	S.D.	2.78	1.70	2.61	2.42
	N	10	10	10	9
DAY 161	INTAKE (g)	19.3	17.8	19.6	20.1
	S.D.	2.50	2.66	2.05	3.98
	N	10	10	10	9
DAY 168	INTAKE (g)	19.7	17.4	20.3	19.5
	S.D.	3.09	2.88	1.52	1.74
	N	10	10	10	9
DAY 175	INTAKE (g)	20.6	20.8	23.5	21.3
	S.D.	1.87	3.88	7.44	4.60
	N	10	10	10	9

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUDY ID: 098 SEX: MALE
ABBR: ALT UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	53	52	56	80	
SD	5.8	9.2	7.2	74.8	
N	10	10	10	10	
Period: Week 4					
MEAN	59	55	56	63	
SD	13.4	10.0	8.0	23.0	
N	10	10	10	10	
Period: Week 8					
MEAN	57	56	71*	65	
SD	18.2	11.0	9.2	7.3	
N	10	10	10	10	
Period: Week 13					
MEAN	60	54	76	79*	
SD	25.6	12.8	14.6	9.7	
N	11	10	10	10	
Period: Week 16					
MEAN	53	47	69	54	
SD	16.0	7.4	18.8	10.6	
N	10	10	10	10	
Period: Week 21					
MEAN	62	57	62	52	
SD	19.2	12.7	14.7	10.1	
N	10	10	10	10	
Period: Week 26					
MEAN	50	72	62	49	
SD	13.6	53.2	31.3	8.0	
N	10	10	10	10	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Aspartate Aminotransferase

STUDY IO: 098 SEX: MALE
ABBR: AST UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	122	109	131	232**	
SD	24.8	14.5	36.0	78.9	
N	10	10	10	10	
Period: Week 4					
MEAN	130	113	124	193**	
SD	21.8	27.6	15.2	58.2	
N	10	10	10	10	
Period: Week 8					
MEAN	107	110	142**	184**	
SD	21.5	20.7	26.8	15.3	
N	10	10	10	10	
Period: Week 13					
MEAN	126	127	175	218**	
SD	28.7	70.4	45.8	32.6	
N	11	10	10	10	
Period: Week 16					
MEAN	114	94	132	115	
SD	44.3	13.6	39.5	23.9	
N	10	10	10	10	
Period: Week 21					
MEAN	115	107	111	102	
SD	28.6	29.5	28.4	26.6	
N	10	10	10	10	
Period: Week 26					
MEAN	87	160	107	85	
SD	18.9	149.9	30.5	8.8	
N	10	10	10	10	

50-160

**-Significant Difference from Control P < .01

Table 11.3

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY ID: 098
ABBR: TP

SEX: MALE
UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	7.6	7.5	7.6	8.1*	
SD	0.36	0.23	0.27	0.53	
N	10	10	10	10	
Period: Week 4					
MEAN	7.8	7.3	7.8	8.3	
SD	0.47	0.36	0.42	0.59	
N	10	10	10	10	
Period: Week 8					
MEAN	7.9	7.8	8.2	8.1	
SD	0.43	0.33	0.36	0.43	
N	10	10	10	10	
Period: Week 13					
MEAN	7.6	7.8	8.0	7.9	
SD	0.19	0.27	0.23	0.58	
N	6	7	3	4	
Period: Week 16					
MEAN	7.9	7.3	7.9	7.7	
SD	0.41	1.03	0.42	0.53	
N	10	10	10	10	
Period: Week 21					
MEAN	8.2	8.0	8.2	7.8	
SD	0.46	0.47	0.46	0.36	
N	10	10	10	10	
Period: Week 26					
MEAN	8.3	8.0	8.3	7.9	
SD	0.41	0.29	0.30	0.48	
N	10	10	10	10	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 098 SEX: MALE
ABBR: ALB UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	4.1	4.0	4.0	4.0	
SD	0.23	0.20	0.18	0.33	
N	10	10	10	10	
Period: Week 4					
MEAN	4.0	4.0	4.2	4.4**	
SD	0.20	0.20	0.19	0.32	
N	10	10	10	10	
Period: Week 8					
MEAN	4.2	4.2	4.4	4.3	
SD	0.35	0.28	0.31	0.44	
N	10	10	10	10	
Period: Week 13					
MEAN	3.9	3.9	4.3*	4.0	
SD	0.19	0.26	0.55	0.30	
N	11	10	10	10	
Period: Week 16					
MEAN	4.2	3.8**	4.2	4.0	
SD	0.13	0.25	0.25	0.27	
N	10	10	10	10	
Period: Week 21					
MEAN	4.5	4.0*	4.2	4.1*	
SD	0.49	0.30	0.24	0.19	
N	10	10	10	10	
Period: Week 26					
MEAN	4.3	4.1	4.2	4.2	
SD	0.23	0.26	0.25	0.28	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 098 SEX: MALE
ABBR: GLOB UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	3.6	3.5	3.6	4.1**	
SD	0.29	0.25	0.23	0.37	
N	10	10	10	10	
Period: Week 4					
MEAN	3.9	3.3*	3.6	3.9	
SD	0.39	0.26	0.45	0.45	
N	10	10	10	10	
Period: Week 8					
MEAN	3.7	3.6	3.9	3.8	
SD	0.49	0.21	0.37	0.38	
N	10	10	10	10	
Period: Week 13					
MEAN	3.8	3.9	4.0	3.8	
SD	0.14	0.21	0.12	0.21	
N	6	7	3	4	
Period: Week 16					
MEAN	3.7	3.5	3.8	3.7	
SD	0.39	1.00	0.43	0.50	
N	10	10	10	10	
Period: Week 21					
MEAN	3.8	3.9	4.0	3.7	
SD	0.49	0.29	0.26	0.21	
N	10	10	10	10	
Period: Week 26					
MEAN	4.0	3.9	4.1	3.6	
SD	0.47	0.37	0.33	0.37	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY IO: 098 SEX: MALE
ABBR: A/G UNITS: -

ANALYSIS OF VARIANCE FOLLOWEO BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1.15	1.14	1.11	1.00*	
SD	0.123	0.133	0.089	0.127	
N	10	10	10	10	
Period: Week 4					
MEAN	1.04	1.21*	1.17	1.15	
SD	0.105	0.098	0.185	0.143	
N	10	10	10	10	
Period: Week 8					
MEAN	1.15	1.15	1.15	1.16	
SD	0.235	0.104	0.185	0.194	
N	10	10	10	10	
Period: Week 13					
MEAN	0.99	0.99	1.01	1.05	
SO	0.041	0.100	0.061	0.078	
N	6	7	3	4	
Period: Week 16					
MEAN	1.13	1.35	1.13	1.11	
SD	0.127	1.156	0.182	0.167	
N	10	10	10	10	
Period: Week 21					
MEAN	1.23	1.03	1.07	1.12	
SD	0.302	0.092	0.057	0.049	
N	10	10	10	10	
Period: Week 26					
MEAN	1.08	1.08	1.02	1.17	
SD	0.183	0.164	0.127	0.130	
N	10	10	10	10	

*-Significant Oifference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bile Acids

STUDY ID: 098
ABBR: TBA

SEX: MALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	54.7	62.8	66.3	40.2	
SD	33.77	31.02	22.72	21.38	
N	10	10	10	10	
Period: Week 4					
MEAN	55.2	46.2	55.8	45.6	
SD	25.89	26.16	38.56	22.47	
N	10	10	10	10	
Period: Week 8					
MEAN	36.0	39.5	43.4	29.2	
SD	17.37	19.08	24.25	12.03	
N	10	10	10	10	
Period: Week 13					
MEAN	43.2	47.9	66.8	50.6	
SD	15.67	29.58	26.93	15.06	
N	11	10	10	10	
Period: Week 16					
MEAN	48.8	55.7	77.9	37.8	
SD	22.86	32.41	45.34	19.39	
N	10	10	10	10	
Period: Week 21					
MEAN	58.1	52.3	42.3	53.7	
SD	42.38	38.69	17.72	25.61	
N	10	10	10	10	
Period: Week 26					
MEAN	44.3	51.1	42.2	41.7	
SD	17.97	27.01	16.83	28.94	
N	10	10	10	10	

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY IO: 098
ABBR: ALKP

SEX: MALE
UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	281	265	256	220**	
SO	53.2	39.2	36.8	32.7	
N	10	10	10	10	
Period: Week 4					
MEAN	230	203	178*	161**	
SD	59.2	23.6	28.0	31.0	
N	10	10	10	10	
Period: Week 8					
MEAN	152	150	133	140	
SO	30.2	31.4	22.5	25.6	
N	10	10	10	10	
Period: Week 13					
MEAN	118	119	116	119	
SO	23.2	39.1	16.7	19.1	
N	11	10	10	10	
Period: Week 16					
MEAN	127	120	128	109	
SD	32.0	35.5	21.7	23.0	
N	10	10	1D	1D	
Period: Week 21					
MEAN	110	117	129	114	
SD	27.2	39.3	32.2	31.4	
N	10	10	10	10	
Period: Week 26					
MEAN	114	119	118	115	
SD	27.6	45.8	39.1	36.9	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Lactate Dehydrogenase

STUDY ID: 098
ABBR: LDH

SEX: MALE
UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	79	128	154	430**	
SD	35.2	105.6	126.9	134.3	
N	9	10	10	10	
Period: Week 4					
MEAN	187	149	122	296*	
SD	109.1	108.4	37.7	109.5	
N	10	10	10	10	
Period: Week 8					
MEAN	144	193	162	239	
SD	207.5	232.9	50.1	28.1	
N	10	10	10	10	
Period: Week 13					
MEAN	293	225	278	297	
SD	261.6	219.6	152.8	98.9	
N	11	10	10	10	
Period: Week 16					
MEAN	155	146	233	100	
SD	127.7	87.3	201.0	71.7	
N	10	10	10	10	
Period: Week 21					
MEAN	269	253	297	141	
SD	177.9	242.4	180.4	125.6	
N	10	10	10	10	
Period: Week 26					
MEAN	130	292	198	85	
SD	75.3	303.0	182.0	54.3	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatine Kinase

STUDY ID: 098
ABBR: CK

SEX: MALE
UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	190	148	301	326	
SD	252.5	105.5	254.5	332.4	
N	10	10	9	10	
Period: Week 4					
MEAN	304	366	150	248	
SD	312.7	662.0	154.5	143.8	
N	10	10	10	10	
Period: Week 8					
MEAN	87	110	126	108	
SD	68.5	87.4	91.9	31.0	
N	10	10	10	10	
Period: Week 13					
MEAN	267	708	120	129	
SD	168.8	1396.8	59.8	106.0	
N	11	10	10	10	
Period: Week 16					
MEAN	428	126	806	112	
SD	768.3	43.0	991.9	78.9	
N	10	10	10	10	
Period: Week 21					
MEAN	256	305	340	138	
SD	156.6	324.4	219.6	72.1	
N	10	10	10	10	
Period: Week 26					
MEAN	143	246	310	160	
SD	92.2	185.6	243.9	145.0	
N	10	10	10	10	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 098 SEX: MALE
ABBR: BUN UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	16.8	15.8	14.9	21.8	
SD	2.14	2.58	3.03	10.88	
N	10	10	10	10	
Period: Week 4					
MEAN	14.7	14.1	11.7*	13.9	
SD	1.94	2.18	1.68	3.07	
N	10	10	10	10	
Period: Week 8					
MEAN	14.7	14.4	12.9	12.2	
SD	2.67	1.21	1.72	3.06	
N	10	10	10	10	
Period: Week 13					
MEAN	15.3	14.3	13.0*	11.9**	
SD	1.42	1.64	2.35	2.08	
N	11	10	10	10	
Period: Week 16					
MEAN	13.4	13.6	12.0	10.6**	
SD	2.21	1.65	1.40	1.83	
N	10	10	10	10	
Period: Week 21					
MEAN	14.3	14.6	13.5	13.3	
SD	1.91	1.93	1.16	2.63	
N	10	10	10	10	
Period: Week 26					
MEAN	14.1	14.6	12.1	13.5	
SD	3.35	3.23	2.54	3.39	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY ID: 098
ABBR: CREA

SEX: MALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.47	0.41	0.48	0.62	
SD	0.054	0.101	0.076	0.250	
N	10	10	10	10	
Period: Week 4					
MEAN	0.51	0.51	0.50	0.52	
SD	0.048	0.062	0.028	0.104	
N	10	10	10	10	
Period: Week 8					
MEAN	0.50	0.51	0.55	0.53	
SD	0.037	0.049	0.061	0.061	
N	10	10	10	10	
Period: Week 13					
MEAN	0.54	0.57	0.59	0.55	
SD	0.045	0.046	0.070	0.063	
N	11	10	10	10	
Period: Week 16					
MEAN	0.53	0.53	0.54	0.51	
SD	0.064	0.034	0.093	0.032	
N	10	10	10	10	
Period: Week 21					
MEAN	0.58	0.56	0.52	0.53	
SD	0.123	0.054	0.033	0.046	
N	10	10	10	10	
Period: Week 26					
MEAN	0.52	0.56	0.49	0.48	
SD	0.051	0.062	0.084	0.038	
N	10	10	10	10	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 098
ABBR: NA

SEX: MALE
UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	146	145	146	145	
SD	2.8	1.4	1.2	1.3	
N	10	10	10	10	
Period: Week 4					
MEAN	145	146	146	146	
SD	1.3	1.6	1.9	2.0	
N	10	10	10	10	
Period: Week 8					
MEAN	147	146	147	146	
SD	1.8	1.7	1.2	1.3	
N	10	10	10	10	
Period: Week 13					
MEAN	146	146	147	146	
SD	1.8	1.9	1.5	1.8	
N	11	10	10	10	
Period: Week 16					
MEAN	146	144	146	146	
SD	2.0	1.7	1.5	1.2	
N	10	10	10	10	
Period: Week 21					
MEAN	145	144	145	145	
SD	2.5	1.6	1.4	0.9	
N	10	10	10	10	
Period: Week 26					
MEAN	146	146	147	145	
SD	1.6	2.1	2.4	2.2	
N	10	10	10	10	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY IO: 098 SEX: MALE
ABBR: K UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	5.87	5.99	6.31	5.90	
SD	0.578	0.525	0.788	0.503	
N	10	10	10	10	
Period: Week 4					
MEAN	5.91	5.84	5.93	6.09	
SD	0.627	0.498	0.465	0.632	
N	10	10	10	10	
Period: Week 8					
MEAN	5.92	5.96	5.74	5.85	
SD	0.307	0.438	0.284	0.352	
N	10	10	10	10	
Period: Week 13					
MEAN	6.06	5.92	5.94	5.73	
SD	0.471	0.307	0.643	0.591	
N	11	10	10	10	
Period: Week 16					
MEAN	5.86	5.88	6.05	5.42	
SD	0.620	0.449	0.510	0.384	
N	10	10	10	10	
Period: Week 21					
MEAN	5.91	5.93	5.94	5.67	
SD	0.468	0.496	0.401	0.419	
N	10	10	10	10	
Period: Week 26					
MEAN	5.88	5.82	6.13	5.60	
SD	0.400	0.450	0.363	0.305	
N	10	10	10	10	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 098
ABBR: CL

SEX: MALE
UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	113	117	117	118	
SD	5.7	4.4	6.0	7.2	
N	10	10	10	10	
Period: Week 4					
MEAN	118	113	116	118	
SD	3.5	4.4	5.5	4.8	
N	10	10	10	10	
Period: Week 8					
MEAN	113	115	115	115	
SD	7.1	3.2	4.9	3.1	
N	10	10	10	10	
Period: Week 13					
MEAN	117	118	116	118	
SD	3.1	4.1	2.5	2.6	
N	11	10	10	10	
Period: Week 16					
MEAN	115	113	116	116	
SD	6.5	9.8	3.4	4.0	
N	10	10	10	10	
Period: Week 21					
MEAN	118	118	118	117	
SD	5.5	4.4	4.9	4.3	
N	10	10	10	10	
Period: Week 26					
MEAN	110	108	113	110	
SD	3.1	3.8	6.5	4.7	
N	10	10	10	10	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 098
ABBR: CA

SEX: MALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	11.6	11.5	11.8	11.6	
SD	0.35	0.81	0.31	0.55	
N	10	10	10	10	
Period: Week 4					
MEAN	11.0	10.8	10.9	11.1	
SD	0.51	0.38	0.35	0.46	
N	10	10	10	10	
Period: Week 8					
MEAN	10.5	10.6	10.6	10.5	
SD	0.48	0.56	0.38	0.40	
N	10	10	10	10	
Period: Week 13					
MEAN	10.5	10.6	10.4	10.6	
SD	0.41	0.33	0.29	0.52	
N	11	10	10	10	
Period: Week 16					
MEAN	11.1	10.8	11.3	10.8	
SD	0.54	0.50	0.49	0.37	
N	10	10	10	10	
Period: Week 21					
MEAN	11.3	11.0	10.6**	10.9	
SD	0.61	0.56	0.26	0.31	
N	10	10	10	10	
Period: Week 26					
MEAN	11.0	10.5*	10.3**	10.8	
SD	0.41	0.41	0.44	0.57	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 098
ABBR: IP

SEX: MALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	10.7	10.5	11.9	10.1	
SD	1.33	1.05	1.85	1.43	
N	10	10	10	10	
Period: Week 4					
MEAN	11.0	9.6	9.4*	10.8	
SD	1.41	0.98	0.81	1.88	
N	9	10	10	10	
Period: Week 8					
MEAN	8.5	8.0	8.1	8.3	
SD	0.68	0.95	0.43	1.05	
N	10	10	10	10	
Period: Week 13					
MEAN	8.8	8.7	8.2	9.0	
SD	1.21	1.35	1.16	1.18	
N	11	10	10	10	
Period: Week 16					
MEAN	8.7	7.9	8.7	8.2	
SD	0.58	1.40	1.99	0.68	
N	10	10	10	10	
Period: Week 21					
MEAN	8.0	7.9	7.6	8.0	
SD	1.09	1.30	0.76	0.83	
N	10	10	10	10	
Period: Week 26					
MEAN	7.4	6.6	7.3	6.8	
SD	1.65	0.97	0.95	0.58	
N	10	10	10	10	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY ID: 098 SEX: MALE
ABBR: GLU UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	139	144	148	146	
SD	20.2	22.1	36.3	33.0	
N	10	10	10	10	
Period: Week 4					
MEAN	194	148*	129**	153*	
SD	42.4	36.2	25.7	42.3	
N	10	10	10	10	
Period: Week 8					
MEAN	128	134	131	115	
SD	8.9	14.8	24.7	9.1	
N	10	10	10	10	
Period: Week 13					
MEAN	157	170	151	130	
SD	47.6	42.4	55.2	23.1	
N	11	10	10	10	
Period: Week 16					
MEAN	167	146	182	120	
SD	36.6	43.5	71.7	14.7	
N	10	10	10	10	
Period: Week 21					
MEAN	177	157	144	145	
SD	51.0	41.8	28.1	38.4	
N	10	10	10	10	
Period: Week 26					
MEAN	143	161	158	140	
SD	11.6	60.0	22.4	13.6	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUDY ID: 098
ABBR: ALT

SEX: FEMALE
UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	55	46	52	54	
SD	12.4	12.3	3.4	11.5	
N	10	10	10	10	
Period: Week 4					
MEAN	57	46	55	61	
SD	13.0	6.9	9.2	13.8	
N	10	10	10	10	
Period: Week 8					
MEAN	56	57	62	64	
SD	10.7	16.0	5.7	8.8	
N	10	10	10	10	
Period: Week 13					
MEAN	64	57	60	68	
SD	18.0	12.2	6.9	11.2	
N	10	10	9	10	
Period: Week 16					
MEAN	70	59	65	44	
SD	34.8	16.7	14.5	10.2	
N	10	10	10	10	
Period: Week 21					
MEAN	72	57	75	60	
SD	34.1	14.2	19.5	21.1	
N	10	10	10	9	
Period: Week 26					
MEAN	68	73	125	118	
SD	19.0	32.9	142.7	85.0	
N	9	10	10	9	

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Aspartate Aminotransferase

STUDY ID: 098
ABBR: AST

SEX: FEMALE
UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	128	113	111	198**	
SD	44.4	23.1	11.1	34.4	
N	10	10	10	10	
Period: Week 4					
MEAN	129	109	117	177**	
SD	42.6	20.8	17.5	31.2	
N	10	10	10	10	
Period: Week 8					
MEAN	114	108	109	192**	
SD	12.8	19.7	9.5	30.1	
N	10	10	10	10	
Period: Week 13					
MEAN	127	141	127	219**	
SD	36.6	45.5	31.9	42.0	
N	10	10	9	10	
Period: Week 16					
MEAN	124	128	129	109	
SD	29.5	50.3	41.2	19.7	
N	10	10	10	10	
Period: Week 21					
MEAN	128	104	120	136	
SD	35.9	18.9	36.9	51.6	
N	10	10	10	9	
Period: Week 26					
MEAN	108	140	203	220	
SD	20.7	76.4	235.7	168.4	
N	9	10	10	9	

**-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY ID: 098
ABBR: TP

SEX: FEMALE
UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	7.8	7.7	7.6	7.5	
SD	0.34	0.51	0.34	0.74	
N	10	10	10	10	
Period: Week 4					
MEAN	7.5	7.8	7.9	7.9	
SD	0.37	0.41	0.64	0.54	
N	10	10	10	10	
Period: Week 8					
MEAN	8.1	8.3	8.2	8.0	
SD	0.46	0.32	0.35	0.32	
N	10	10	10	10	
Period: Week 13					
MEAN	8.2	8.0	7.8	8.0	
SD	0.35	0.55	0.66	0.28	
N	7	6	5	2	
Period: Week 16					
MEAN	8.7	8.4	8.7	8.0*	
SD	0.59	0.75	0.36	0.49	
N	10	10	10	10	
Period: Week 21					
MEAN	9.0	8.6	9.3	8.1*	
SD	0.70	0.76	0.61	0.51	
N	10	10	10	9	
Period: Week 26					
MEAN	9.1	9.1	9.1	8.6	
SD	0.38	1.00	0.44	0.41	
N	10	10	10	9	

*-Significant Difference from Control P < .05

Table 12.4
THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 098
ABBR: ALB

SEX: FEMALE
UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	4.1	4.0	4.0	3.7**	
SD	0.19	0.30	0.20	0.51	
N	10	10	10	10	
Period: Week 4					
MEAN	4.2	4.3	4.2	4.1	
SD	0.27	0.18	0.27	0.34	
N	10	10	10	10	
Period: Week 8					
MEAN	4.3	4.4	4.4	4.4	
SD	0.34	0.36	0.34	0.24	
N	10	10	10	10	
Period: Week 13					
MEAN	4.4	4.3	4.2	4.0	
SD	0.51	0.35	0.32	0.37	
N	10	10	9	10	
Period: Week 16					
MEAN	4.6	4.5	4.7	4.2	
SD	0.42	0.56	0.22	0.26	
N	10	10	10	10	
Period: Week 21					
MEAN	4.8	4.7	5.1	4.3	
SD	0.56	0.51	0.51	0.26	
N	10	10	10	9	
Period: Week 26					
MEAN	5.1	5.1	5.2	4.8	
SD	0.35	0.70	0.35	0.21	
N	10	10	10	9	

**-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 098
ABBR: GLOB

SEX: FEMALE
UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	3.7	3.7	3.6	3.8	
SD	0.30	0.36	0.34	0.30	
N	10	10	10	10	
Period: Week 4					
MEAN	3.3	3.5	3.7	3.8*	
SD	0.29	0.29	0.48	0.47	
N	10	10	10	10	
Period: Week 8					
MEAN	3.7	3.9	3.7	3.6	
SD	0.32	0.34	0.39	0.45	
N	10	10	10	10	
Period: Week 13					
MEAN	3.9	3.9	3.7	4.0	
SD	0.25	0.35	0.42	0.07	
N	7	6	5	2	
Period: Week 16					
MEAN	4.1	3.9	4.0	3.8	
SD	0.35	0.51	0.39	0.41	
N	10	10	10	10	
Period: Week 21					
MEAN	4.1	3.9	4.2	3.8	
SD	0.32	0.38	0.19	0.38	
N	10	10	10	9	
Period: Week 26					
MEAN	4.0	4.1	3.9	3.8	
SD	0.48	0.60	0.41	0.32	
N	10	10	10	9	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY ID: 098
ABBR: A/G

SEX: FEMALE
UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1.11	1.11	1.14	0.96*	
SD	0.103	0.112	0.136	0.108	
N	10	10	10	10	
Period: Week 4					
MEAN	1.27	1.25	1.15	1.08**	
SD	0.141	0.085	0.137	0.161	
N	10	10	10	10	
Period: Week 8					
MEAN	1.17	1.15	1.20	1.25	
SD	0.133	0.175	0.196	0.242	
N	10	10	10	10	
Period: Week 13					
MEAN	1.12	1.06	1.10	1.03	
SD	0.086	0.101	0.115	0.106	
N	7	6	5	2	
Period: Week 16					
MEAN	1.13	1.19	1.20	1.13	
SD	0.134	0.213	0.153	0.130	
N	10	10	10	10	
Period: Week 21					
MEAN	1.18	1.23	1.22	1.16	
SD	0.137	0.140	0.112	0.116	
N	10	10	10	9	
Period: Week 26					
MEAN	1.32	1.28	1.36	1.28	
SD	0.236	0.259	0.191	0.115	
N	10	10	10	9	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bile Acids

STUDY ID: 098
ABBR: TBA

SEX: FEMALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	54.1	43.7	61.7	54.1	
SD	45.69	26.19	62.52	47.24	
N	10	10	10	10	
Period: Week 4					
MEAN	49.8	67.3	43.9	43.6	
SD	46.84	59.22	28.16	27.38	
N	10	10	10	10	
Period: Week 8					
MEAN	26.2	45.3	37.8	42.4	
SD	10.82	44.36	20.94	30.90	
N	10	10	10	10	
Period: Week 13					
MEAN	42.1	38.6	34.9	59.9	
SD	20.93	14.83	27.40	46.96	
N	10	10	9	10	
Period: Week 16					
MEAN	25.6	28.9	45.6	54.3	
SD	10.16	12.48	39.19	79.88	
N	10	10	10	10	
Period: Week 21					
MEAN	30.4	26.2	69.6	48.9	
SD	11.15	10.09	123.70	35.29	
N	10	10	10	9	
Period: Week 26					
MEAN	34.3	40.4	81.9	59.5	
SD	38.05	21.53	81.98	59.77	
N	10	10	10	9	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY ID: 098
ABBR: ALKP

SEX: FEMALE
UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	199	189	201	188	
SD	42.7	35.8	42.7	85.2	
N	10	10	10	10	
Period: Week 4					
MEAN	147	158	145	118	
SD	30.7	23.0	32.3	33.0	
N	10	10	10	10	
Period: Week 8					
MEAN	100	108	100	88	
SD	19.8	15.6	23.0	18.4	
N	10	10	10	10	
Period: Week 13					
MEAN	76	72	76	87	
SD	19.2	11.3	26.5	67.9	
N	10	10	9	10	
Period: Week 16					
MEAN	74	71	88	71	
SD	20.6	13.5	21.3	21.4	
N	10	10	10	10	
Period: Week 21					
MEAN	63	64	67	65	
SD	16.5	14.0	20.2	20.8	
N	10	10	10	9	
Period: Week 26					
MEAN	64	62	62	68	
SD	22.6	13.2	19.5	23.2	
N	10	10	10	9	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Lactate Dehydrogenase

STUDY IO: 098 SEX: FEMALE
ABBR: LDH UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	93	180	118	409**	
SD	96.4	125.8	123.5	180.5	
N	9	10	10	10	
Period: Week 4					
MEAN	196	141	218	224	
SD	126.0	92.8	205.8	63.9	
N	10	10	10	10	
Period: Week 8					
MEAN	263	111*	135	262	
SD	150.1	77.5	130.2	111.0	
N	10	10	10	10	
Period: Week 13					
MEAN	252	297	312	334	
SD	161.1	207.2	486.0	116.0	
N	10	10	9	10	
Period: Week 16					
MEAN	282	249	240	118	
SD	244.8	166.5	209.5	63.2	
N	10	10	10	10	
Period: Week 21					
MEAN	291	263	215	245	
SD	222.4	129.3	105.5	121.0	
N	10	10	10	9	
Period: Week 26					
MEAN	150	350	186	168	
SD	113.6	261.6	208.5	168.0	
N	10	10	10	9	

*-Significant Oifference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatine Kinase

STUDY ID: 098
ABBR: CK

SEX: FEMALE
UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	307	287	140	150	
SD	412.4	214.7	109.2	88.6	
N	10	10	10	10	
Period: Week 4					
MEAN	224	170	197	215	
SD	126.6	104.1	124.3	134.6	
N	10	10	10	10	
Period: Week 8					
MEAN	163	113	105	234	
SD	57.0	58.5	69.1	251.3	
N	10	10	10	10	
Period: Week 13					
MEAN	392	477	351	319	
SD	349.1	427.8	361.2	349.1	
N	10	10	9	10	
Period: Week 16					
MEAN	178	366	301	208	
SD	112.0	324.6	329.3	129.8	
N	10	10	10	10	
Period: Week 21					
MEAN	269	278	206	250	
SD	172.1	176.4	170.2	99.7	
N	10	10	10	9	
Period: Week 26					
MEAN	164	349	152	125	
SD	174.9	239.2	106.7	112.4	
N	10	8	10	9	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 098
ABBR: BUN

SEX: FEMALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	14.7	16.6	16.4	14.2	
SD	2.98	2.33	2.20	4.48	
N	10	10	10	10	
Period: Week 4					
MEAN	13.7	15.4	16.5*	14.8	
SD	1.85	2.43	1.00	2.95	
N	10	10	10	10	
Period: Week 8					
MEAN	13.5	13.9	14.0	14.6	
SD	2.17	2.60	2.89	2.66	
N	10	10	10	10	
Period: Week 13					
MEAN	12.9	14.5	14.0	14.0	
SD	1.30	2.38	1.80	2.28	
N	10	10	9	10	
Period: Week 16					
MEAN	12.3	13.8	14.6*	11.9	
SD	1.50	2.96	1.37	1.94	
N	10	10	10	10	
Period: Week 21					
MEAN	14.5	14.0	14.5	15.2	
SD	2.00	1.76	1.67	2.04	
N	10	10	10	9	
Period: Week 26					
MEAN	11.6	15.1	14.2	13.9	
SD	2.42	5.21	2.67	3.18	
N	10	10	10	9	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY IO: 098 SEX: FEMALE
ABBR: CREA UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.49	0.48	0.49	0.46	
SD	0.070	0.044	0.065	0.092	
N	10	10	10	10	
Period: Week 4					
MEAN	0.54	0.54	0.57	0.49	
SD	0.101	0.051	0.079	0.049	
N	10	10	10	10	
Period: Week 8					
MEAN	0.57	0.56	0.58	0.57	
SD	0.076	0.035	0.057	0.045	
N	10	10	10	10	
Period: Week 13					
MEAN	0.62	0.64	0.64	0.61	
SD	0.064	0.099	0.044	0.030	
N	10	10	9	10	
Period: Week 16					
MEAN	0.60	0.61	0.61	0.55*	
SD	0.044	0.046	0.040	0.037	
N	10	10	10	10	
Period: Week 21					
MEAN	0.63	0.62	0.62	0.57**	
SD	0.047	0.035	0.048	0.046	
N	9	10	10	9	
Period: Week 26					
MEAN	0.58	0.64	0.59	0.57	
SD	0.056	0.127	0.043	0.049	
N	10	10	10	9	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 098
ABBR: NA

SEX: FEMALE
UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	144	144	144	143	
SD	1.5	1.5	2.0	2.4	
N	10	10	10	10	
Period: Week 4					
MEAN	144	145	143	143	
SD	1.6	1.1	2.3	1.2	
N	10	10	10	10	
Period: Week 8					
MEAN	143	145	145	144	
SD	1.2	1.3	1.6	1.6	
N	10	9	10	10	
Period: Week 13					
MEAN	145	147*	145	144	
SD	1.7	2.1	1.5	1.1	
N	10	10	9	10	
Period: Week 16					
MEAN	144	144	145	144	
SD	1.9	1.3	1.5	1.7	
N	10	10	10	10	
Period: Week 21					
MEAN	143	144	144	142	
SD	1.8	1.5	2.4	1.9	
N	10	10	10	9	
Period: Week 26					
MEAN	146	145	145	145	
SD	1.8	1.2	2.3	1.0	
N	10	10	10	9	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY ID: 098 SEX: FEMALE
ABBR: K UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	5.61	5.96	5.77	5.83	
SD	0.455	0.485	0.407	0.414	
N	10	10	10	10	
Period: Week 4					
MEAN	5.72	5.80	5.64	5.65	
SD	0.369	0.608	0.511	0.298	
N	10	10	10	10	
Period: Week 8					
MEAN	5.68	6.00	5.63	5.83	
SD	0.539	0.863	0.358	0.695	
N	10	10	10	10	
Period: Week 13					
MEAN	5.85	5.94	5.47	5.70	
SD	0.245	0.596	0.488	0.635	
N	10	10	9	10	
Period: Week 16					
MEAN	5.66	5.81	5.59	5.48	
SD	0.290	0.328	0.462	0.351	
N	10	10	10	10	
Period: Week 21					
MEAN	5.65	5.68	5.61	5.55	
SD	0.282	0.483	0.408	0.289	
N	10	10	10	9	
Period: Week 26					
MEAN	5.45	5.49	5.35	5.29	
SD	0.340	0.310	0.264	0.421	
N	10	10	10	9	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 098
ABBR: CL

SEX: FEMALE
UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	118	117	116	120	
SD	6.3	4.7	5.2	4.5	
N	10	10	10	10	
Period: Week 4					
MEAN	115	114	119	116	
SD	4.7	4.3	5.9	5.2	
N	10	10	10	10	
Period: Week 8					
MEAN	115	113	118	118	
SD	4.4	4.0	7.3	4.7	
N	10	10	10	10	
Period: Week 13					
MEAN	117	118	115	121	
SD	3.5	2.7	11.8	3.0	
N	10	10	9	10	
Period: Week 16					
MEAN	116	117	116	116	
SD	3.6	4.6	4.3	4.8	
N	10	10	10	10	
Period: Week 21					
MEAN	120	117	119	120	
SD	4.9	3.7	2.2	4.1	
N	10	10	10	9	
Period: Week 26					
MEAN	110	112	108	110	
SD	4.4	3.2	4.0	4.8	
N	10	10	10	9	

Table 12.16

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 098
ABBR: CA

SEX: FEMALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	11.7	11.5	11.7	11.6	
SD	0.22	0.56	0.45	0.67	
N	10	10	10	10	
Period: Week 4					
MEAN	10.9	11.2	10.8	10.7	
SD	0.40	0.58	0.59	0.50	
N	10	10	10	10	
Period: Week 8					
MEAN	10.6	10.5	10.7	10.7	
SD	0.60	0.69	0.51	0.33	
N	10	10	10	10	
Period: Week 13					
MEAN	10.9	10.3	10.5	10.5	
SD	0.50	0.87	0.35	0.58	
N	10	10	9	10	
Period: Week 16					
MEAN	11.0	10.9	10.9	10.7	
SD	0.59	0.64	0.39	0.49	
N	10	10	10	10	
Period: Week 21					
MEAN	11.2	10.8	10.9	10.5**	
SD	0.44	0.45	0.50	0.33	
N	10	10	10	9	
Period: Week 26					
MEAN	11.0	10.9	11.3	10.7	
SD	0.50	0.57	0.65	0.50	
N	10	10	10	9	

**-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 098
ABBR: IP

SEX: FEMALE
UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	10.0	10.0	9.8	9.3	
SD	0.98	1.14	1.55	1.20	
N	10	10	10	10	
Period: Week 4					
MEAN	9.5	10.0	10.3	9.4	
SD	1.25	2.27	1.78	0.87	
N	10	10	10	10	
Period: Week 8					
MEAN	7.7	7.7	7.7	8.1	
SD	0.91	1.48	0.80	1.31	
N	10	10	10	10	
Period: Week 13					
MEAN	9.0	8.2	8.2	8.5	
SD	2.16	1.33	1.26	1.62	
N	10	10	9	9	
Period: Week 16					
MEAN	7.1	7.1	7.0	7.2	
SD	1.07	1.50	1.01	1.01	
N	10	10	10	10	
Period: Week 21					
MEAN	7.3	6.9	6.5	7.1	
SD	1.63	1.25	1.23	1.02	
N	10	10	10	9	
Period: Week 26					
MEAN	5.7	5.9	5.7	5.8	
SD	0.81	0.99	1.14	1.48	
N	10	10	10	9	

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY IO: 098 SEX: FEMALE
ABBR: GLU UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEOURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	149	141	142	143	
SD	28.0	26.6	17.0	24.8	
N	10	10	10	10	
Period: Week 4					
MEAN	148	143	143	133	
SD	33.7	20.8	14.7	25.2	
N	10	10	10	10	
Period: Week 8					
MEAN	137	134	130	118*	
SD	16.2	14.8	18.4	9.9	
N	10	10	10	10	
Period: Week 13					
MEAN	157	151	148	140	
SD	20.4	34.1	42.2	32.5	
N	10	10	9	10	
Period: Week 16					
MEAN	144	147	143	118	
SD	26.2	31.4	30.4	13.9	
N	10	10	10	10	
Period: Week 21					
MEAN	145	142	131	137	
SD	40.2	26.6	22.0	16.9	
N	10	10	10	9	
Period: Week 26					
MEAN	127	154	134	138	
SD	12.9	31.3	24.8	25.2	
N	10	10	10	9	

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Erythrocytes

STUDY ID: 098
ABBR: RBC

SEX: MALE
UNITS: 10^6/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	7.30	7.21	7.22	6.56**	
SD	0.385	0.293	0.496	0.533	
N	10	10	10	10	
Period: Week 4					
MEAN	7.68	7.54	7.30	7.16*	
SD	0.442	0.473	0.238	0.500	
N	10	10	10	10	
Period: Week 8					
MEAN	8.09	8.11	7.78	7.76	
SD	0.386	0.262	0.330	0.390	
N	10	10	10	10	
Period: Week 13					
MEAN	8.11	8.13	8.00	7.86	
SD	0.420	0.619	0.427	0.333	
N	11	10	9	10	
Period: Week 16					
MEAN	8.20	8.00	8.07	7.95	
SD	0.442	0.162	0.568	0.521	
N	10	10	10	10	
Period: Week 21					
MEAN	8.55	8.39	8.94	8.79	
SD	0.406	0.415	0.383	0.539	
N	10	10	10	10	
Period: Week 27					
MEAN	8.19	8.27	8.45	8.42	
SD	0.507	0.305	0.349	0.554	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hemoglobin

STUOY IO: 098 SEX: MALE
ABBR: THGB UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	15.6	15.4	15.4	13.7**	
SD	0.67	0.64	0.75	0.79	
N	10	10	10	10	
Period: Week 4					
MEAN	16.2	15.8	15.3*	14.4**	
SD	0.76	0.76	0.61	0.75	
N	10	10	10	10	
Period: Week 8					
MEAN	16.3	16.5	15.2**	14.4**	
SD	1.01	0.51	0.56	0.77	
N	10	10	10	10	
Period: Week 13					
MEAN	15.9	15.5	15.3	14.2	
SD	0.80	2.76	0.59	0.81	
N	11	10	9	10	
Period: Week 16					
MEAN	16.1	15.9	15.5	15.0**	
SD	0.91	0.38	0.76	0.68	
N	10	10	10	10	
Period: Week 21					
MEAN	16.2	16.1	16.2	16.0	
SD	0.64	0.67	0.82	0.50	
N	10	10	10	10	
Period: Week 27					
MEAN	15.6	15.9	15.8	15.7	
SD	0.83	0.60	0.64	0.57	
N	10	10	10	10	

*-Significant Oifference from Control P < .05 **-Significant Difference from Control P < .01

SUMMARY OF HEMATOLOGY TESTS
TEST: Hematocrit

STUDY ID: 098
ABBR: HCT

SEX: MALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	44.7	44.3	44.1	39.2**	
SD	1.99	1.82	2.51	2.46	
N	10	10	10	10	
Period: Week 4					
MEAN	45.8	45.1	43.6*	41.8**	
SD	2.19	2.24	1.75	1.86	
N	10	10	10	10	
Period: Week 8					
MEAN	44.8	45.6	43.1	41.3**	
SD	2.61	1.65	1.34	2.02	
N	10	10	10	10	
Period: Week 13					
MEAN	43.0	44.2	42.3	40.5	
SD	2.38	3.39	1.95	2.53	
N	11	10	9	10	
Period: Week 16					
MEAN	44.2	43.9	43.3	42.4	
SD	2.40	1.53	2.97	2.05	
N	10	10	10	10	
Period: Week 21					
MEAN	45.1	45.2	45.6	44.6	
SD	1.97	2.21	2.42	1.85	
N	10	10	10	10	
Period: Week 27					
MEAN	42.8	44.0	43.7	43.6	
SD	3.45	2.15	2.08	1.76	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 098
ABBR: MCV

SEX: MALE
UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	61.3	61.5	61.2	59.9	
SD	1.96	1.82	1.60	2.60	
N	10	10	10	10	
Period: Week 4					
MEAN	59.7	59.9	59.7	58.5	
SD	1.90	1.87	1.69	2.66	
N	10	10	10	10	
Period: Week 8					
MEAN	55.4	56.2	55.5	53.3	
SD	2.31	1.74	1.68	3.01	
N	10	10	10	10	
Period: Week 13					
MEAN	53.1	54.4	52.9	51.5	
SD	2.66	1.67	1.02	3.02	
N	11	10	9	10	
Period: Week 16					
MEAN	54.0	54.8	53.6	53.5	
SD	2.66	1.39	1.18	3.44	
N	10	10	10	10	
Period: Week 21					
MEAN	52.9	54.0	51.0	50.8	
SD	2.89	1.48	0.94	2.30	
N	10	10	10	10	
Period: Week 27					
MEAN	52.2	53.2	51.7	51.8	
SD	2.72	1.58	1.16	2.38	
N	10	10	10	10	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemoglobin

STUDY ID: 098
ABBR: TMCH

SEX: MALE
UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	21.4	21.4	21.3	20.9	
SD	0.64	0.41	0.59	1.05	
N	10	10	10	10	
Period: Week 4					
MEAN	21.1	21.0	21.0	20.1*	
SD	0.79	0.65	0.60	0.96	
N	10	10	10	10	
Period: Week 8					
MEAN	20.1	20.4	19.6	18.6**	
SD	0.89	0.74	0.43	1.08	
N	10	10	10	10	
Period: Week 13					
MEAN	19.6	18.9	19.1	18.1	
SD	1.06	2.54	0.55	0.99	
N	11	10	9	10	
Period: Week 16					
MEAN	19.7	19.9	19.2	18.9	
SD	1.14	0.42	0.82	1.10	
N	10	10	10	10	
Period: Week 21					
MEAN	19.0	19.3	18.2*	18.2	
SD	0.92	0.50	0.42	0.87	
N	10	10	10	10	
Period: Week 27					
MEAN	19.1	19.2	18.7	18.6	
SD	1.01	0.59	0.41	0.82	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemo. Conc.

STUDY ID: 098
ABBR: TMCHC

SEX: MALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	35.0	34.9	34.9	34.9	
SD	0.60	0.76	0.53	0.70	
N	10	10	10	10	
Period: Week 4					
MEAN	35.4	35.1	35.2	34.4**	
SD	0.71	0.35	0.58	0.71	
N	10	10	10	10	
Period: Week 8					
MEAN	36.3	36.3	35.3**	34.9**	
SD	0.74	0.53	0.76	0.75	
N	10	10	10	10	
Period: Week 13					
MEAN	36.9	34.8	36.2	35.1	
SD	1.30	4.72	0.67	0.75	
N	11	10	9	10	
Period: Week 16					
MEAN	36.5	36.2	35.8	35.3**	
SD	0.49	0.55	1.11	0.63	
N	10	10	10	10	
Period: Week 21					
MEAN	35.9	35.7	35.6	35.9	
SD	0.68	0.63	0.44	0.46	
N	10	10	10	10	
Period: Week 27					
MEAN	36.6	36.2	36.1	36.0	
SD	1.62	0.72	0.60	0.25	
N	10	10	10	10	

**-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Reticulocytes Count

STUDY IO: 098 SEX: MALE
ABBR: RETICS UNITS: % RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEOURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1.2	1.8	1.5	4.0**	
SO	0.59	0.60	0.93	1.28	
N	10	10	10	10	
Period: Week 4					
MEAN	0.5	1.0	0.8	1.9**	
SD	0.41	0.36	0.46	1.28	
N	10	10	10	10	
Period: Week 8					
MEAN	0.8	0.9	1.6*	2.4**	
SD	0.42	0.69	0.72	1.00	
N	10	9	10	10	
Period: Week 13					
MEAN	0.6	0.8	1.5**	1.8**	
SO	0.22	0.47	0.93	0.67	
N	11	10	9	10	
Period: Week 16					
MEAN	0.9	0.7	1.1	1.0	
SO	0.44	0.41	0.54	0.38	
N	10	10	10	10	
Period: Week 21					
MEAN	0.5	0.4	0.3	0.3	
SD	0.28	0.35	0.29	0.18	
N	10	10	10	10	
Period: Week 27					
MEAN	0.8	0.6	0.7	0.6	
SD	0.18	0.27	0.40	0.35	
N	10	10	10	10	

*-Significant Oifference from Control P < .05 **-Significant Oifference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Nucleated Red Cells

STUDY ID: 098
ABBR: NRBC

SEX: MALE
UNITS: COUNT

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.3	
N	10	10	10	10	
Period: Week 4					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.0	
N	10	10	10	10	
Period: Week 8					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.4	
N	10	10	10	10	
Period: Week 13					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.3	
N	11	10	9	10	
Period: Week 16					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.0	
N	10	10	10	10	
Period: Week 21					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.0	
N	10	10	10	10	
Period: Week 27					
MEAN	0	0	0	0	
SD	0.0	0.0	0.3	0.0	
N	10	10	10	10	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Heinz Bodies

STUDY ID: 098 SEX: MALE
ABBR: HB UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.0	0.0	0.0	2.3**	
SD	0.00	0.03	0.05	0.91	
N	10	10	10	10	
Period: Week 4					
MEAN	0.0	0.1	0.6*	0.6*	
SD	0.00	0.22	0.73	0.38	
N	10	10	10	10	
Period: Week 8					
MEAN	0.1	0.1	0.1	0.3	
SD	0.31	0.12	0.08	0.32	
N	10	10	10	10	
Period: Week 13					
MEAN	0.0	0.0	0.3*	0.8**	
SD	0.00	0.00	0.32	0.32	
N	11	10	9	10	
Period: Week 16					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.04	
N	10	10	10	10	
Period: Week 21					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.09	
N	10	10	10	10	
Period: Week 27					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: % Methemoglobin

STUDY ID: 098 SEX: MALE
ABBR: %METHGB UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.4	0.5	2.0	15.5**	
SD	0.43	0.38	1.15	9.22	
N	10	10	10	10	
Period: Week 4					
MEAN	0.7	0.4	4.4**	9.7**	
SD	0.71	0.29	0.78	2.54	
N	10	10	10	10	
Period: Week 8					
MEAN	0.4	0.5	6.7**	9.5**	
SD	0.36	0.31	0.88	1.48	
N	10	10	10	10	
Period: Week 13					
MEAN	0.5	0.5	7.0**	12.0**	
SD	0.34	0.35	1.06	1.17	
N	10	10	9	10	
Period: Week 16					
MEAN	0.3	0.3	0.4	1.3**	
SD	0.35	0.33	0.36	0.88	
N	10	10	10	10	
Period: Week 21					
MEAN	0.4	0.5	0.6	0.5	
SD	0.39	0.33	0.74	0.51	
N	10	10	10	10	
Period: Week 27					
MEAN	0.3	0.7	0.9*	0.7	
SD	0.30	0.28	0.56	0.36	
N	10	10	10	10	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Platelets

STUDY ID: 098
ABBR: PLT

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1209	1268	1120	1196	
SD	108.8	141.3	138.9	358.4	
N	10	10	10	10	
Period: Week 4					
MEAN	1146	1173	1169	1069	
SD	103.3	152.7	114.2	192.4	
N	10	10	10	10	
Period: Week 8					
MEAN	1140	1153	1107	1061	
SD	74.0	124.8	95.0	144.2	
N	10	10	10	10	
Period: Week 13					
MEAN	1042	1092	1014	950	
SD	139.4	209.3	143.0	139.3	
N	11	10	9	10	
Period: Week 16					
MEAN	1005	1025	964	962	
SD	205.3	193.3	203.6	129.9	
N	10	10	10	10	
Period: Week 21					
MEAN	1038	1074	1091	929	
SD	175.0	194.7	103.7	90.3	
N	10	10	10	10	
Period: Week 27					
MEAN	1091	1097	1052	1006	
SD	160.2	227.2	153.3	76.3	
N	10	10	10	10	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Act. Partial Thrombo. Time

STUDY ID: 098
ABBR: APTT

SEX: MALE
UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 14					
MEAN	16.2	15.3	13.8	15.8	
SD	2.13	2.26	1.96	4.06	
N	10	10	10	5	
Period: Week 27					
MEAN	15.1	14.5	15.4	14.8	
SD	1.78	1.98	2.18	2.20	
N	10	10	10	10	

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Leukocytes

STUDY ID: 098
ABBR: WBC

SEX: MALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	17.8	19.1	20.6	28.0**	
SD	3.99	4.63	2.71	7.38	
N	10	10	10	10	
Period: Week 4					
MEAN	17.6	15.8	24.0**	24.5**	
SD	3.57	4.13	2.98	2.24	
N	10	10	10	10	
Period: Week 8					
MEAN	16.9	16.6	22.9**	22.5**	
SD	2.96	4.17	3.14	3.25	
N	10	10	10	10	
Period: Week 13					
MEAN	14.2	14.7	23.4**	27.6**	
SD	2.10	3.03	3.73	7.35	
N	11	10	9	10	
Period: Week 16					
MEAN	13.8	12.6	13.6	18.6**	
SD	2.96	2.88	2.03	5.02	
N	10	10	10	10	
Period: Week 21					
MEAN	14.1	13.9	13.0	14.4	
SD	3.40	2.74	2.31	2.46	
N	10	10	10	10	
Period: Week 27					
MEAN	12.9	14.1	12.9	14.0	
SD	2.41	4.42	1.97	2.50	
N	10	10	10	10	

WBC corrected for NRBC = or > 10

**-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: M. Neutrophils

STUDY ID: 098
ABBR: M. Neutrop

SEX: MALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1.6	1.9	2.5	5.6**	
SD	0.67	0.82	1.02	3.22	
N	10	10	10	10	
Period: Week 4					
MEAN	1.4	1.6	3.4**	2.4*	
SD	0.53	0.58	1.16	0.81	
N	10	10	10	10	
Period: Week 8					
MEAN	2.4	1.7	2.9	3.1	
SD	1.69	0.78	0.69	1.49	
N	10	10	10	10	
Period: Week 13					
MEAN	1.8	2.0	3.2**	4.6**	
SD	0.80	0.53	0.66	0.88	
N	11	10	9	10	
Period: Week 16					
MEAN	1.3	1.2	1.9	4.1	
SD	0.50	0.48	0.70	5.16	
N	10	10	10	10	
Period: Week 21					
MEAN	1.4	2.8	1.3	1.7	
SD	0.43	3.98	0.46	0.84	
N	10	10	10	10	
Period: Week 27					
MEAN	1.7	2.3	1.8	1.8	
SD	0.71	1.69	0.72	0.97	
N	10	10	10	10	

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05
**-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: I. Neutrophils

STUDY ID: 098
ABBR: I. Neutrop

SEX: MALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 4					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.04	0.00	0.00	
N	10	10	10	10	
Period: Week 8					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 13					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	11	10	9	10	
Period: Week 16					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 21					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 27					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Lymphocytes

STUDY ID: 098
ABBR: Lymphocyte

SEX: MALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	15.8	16.3	17.4	21.0	
SD	3.83	4.71	2.65	7.69	
N	10	10	10	10	
Period: Week 4					
MEAN	15.8	13.8	19.0	18.7	
SD	3.33	4.00	2.90	2.48	
N	10	10	10	10	
Period: Week 8					
MEAN	13.4	13.8	18.5**	17.1*	
SD	3.07	3.43	2.62	3.36	
N	10	10	10	10	
Period: Week 13					
MEAN	11.6	12.1	18.8**	20.2**	
SD	2.44	2.85	3.27	6.71	
N	11	10	9	10	
Period: Week 16					
MEAN	11.9	10.5	11.0	13.3	
SD	2.92	2.77	1.96	5.83	
N	10	10	10	10	
Period: Week 21					
MEAN	12.0	10.5	11.1	12.2	
SD	3.39	4.01	1.94	2.21	
N	10	10	10	10	
Period: Week 27					
MEAN	10.6	11.1	10.3	11.5	
SD	2.07	2.81	1.52	1.72	
N	10	10	10	10	

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05
**-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Monocytes

STUDY IO: 098 SEX: MALE
ABBR: Monocytes UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.4	0.7	0.7	1.3**	
SD	0.21	0.49	0.39	1.03	
N	10	10	10	10	
Period: Week 4					
MEAN	0.3	0.3	1.5	3.4**	
SD	0.29	0.14	0.99	2.55	
N	10	10	10	10	
Period: Week 8					
MEAN	0.8	1.0	1.4	2.2**	
SD	0.47	0.47	0.89	0.70	
N	10	10	10	10	
Period: Week 13					
MEAN	0.6	0.4	1.4*	2.9**	
SD	0.41	0.22	0.87	1.09	
N	11	10	9	10	
Period: Week 16					
MEAN	0.5	0.8	0.5	1.1*	
SD	0.34	0.47	0.31	0.73	
N	10	10	10	10	
Period: Week 21					
MEAN	0.5	0.4	0.5	0.4	
SD	0.39	0.21	0.41	0.29	
N	10	10	10	10	
Period: Week 27					
MEAN	0.5	0.6	0.7	0.5	
SD	0.23	0.45	0.51	0.32	
N	10	10	10	10	

WBC corrected for NRBC = or > 10
**-Significant Difference from Control P < .01
*-Significant Difference from Control P < .05

SUMMARY OF HEMATOLOGY TESTS
TEST: Eosinophils

STUDY ID: 098
ABBR: Eosinophil

SEX: MALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.1	0.2	0.1	0.1	
SD	0.10	0.28	0.13	0.11	
N	10	10	10	10	
Period: Week 4					
MEAN	0.1	0.1	0.3*	0.1	
SD	0.13	0.21	0.14	0.12	
N	10	10	10	10	
Period: Week 8					
MEAN	0.2	0.1	0.1	0.1	
SD	0.20	0.13	0.12	0.17	
N	10	10	10	10	
Period: Week 13					
MEAN	0.1	0.1	0.0	0.0*	
SD	0.14	0.11	0.07	0.00	
N	11	10	9	10	
Period: Week 16					
MEAN	0.1	0.1	0.1	0.1	
SD	0.09	0.13	0.13	0.10	
N	10	10	10	10	
Period: Week 21					
MEAN	0.2	0.2	0.0	0.1	
SD	0.16	0.19	0.04	0.11	
N	10	10	10	10	
Period: Week 27					
MEAN	0.2	0.1	0.1	0.1	
SD	0.14	0.16	0.10	0.12	
N	10	10	10	10	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

SUMMARY OF HEMATOLOGY TESTS
TEST: Basophils

STUDY ID: 098
ABBR: Basophils

SEX: MALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 4					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 8					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 13					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	11	10	9	10	
Period: Week 16					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 21					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 27					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	

WBC corrected for NRBC = or > 10

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Erythrocytes

STUDY ID: 098 SEX: FEMALE
ABBR: RBC UNITS: 10^6/cmm

ANALYSIS DF VARIANCE FDLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0 mg base/kg/day
Period: Week 2				
MEAN	7.28	7.04	6.98	6.19**
SD	0.301	0.353	0.282	0.365
N	10	10	1D	10
Period: Week 4				
MEAN	7.39	7.34	6.97*	6.86**
SD	0.357	0.4D2	D.313	0.370
N	10	10	10	10
Period: Week 8				
MEAN	7.86	7.76	7.26**	7.54
SD	0.159	0.465	0.367	0.388
N	10	1D	1D	10
Period: Week 13				
MEAN	7.87	7.68	7.23*	6.85**
SD	0.298	0.427	0.416	0.769
N	9	10	9	10
Period: Week 16				
MEAN	7.68	7.42	7.39	7.55
SD	0.360	0.355	0.599	0.358
N	10	9	9	10
Period: Week 21				
MEAN	8.11	7.97	8.DO	8.29
SD	0.354	0.337	0.349	D.233
N	10	10	10	9
Period: Week 27				
MEAN	7.8D	7.62	7.73	7.77
SD	0.403	0.432	0.322	0.398
N	10	10	10	9

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hemoglobin

STUDY ID: 098 SEX: FEMALE
ABBR: THGB UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0 mg base/kg/day
Period: Week 2				
MEAN	15.8	15.4	15.1*	13.1**
SD	0.46	0.66	0.49	0.82
N	10	10	10	10
Period: Week 4				
MEAN	15.7	15.8	15.3	14.1**
SD	0.50	0.67	0.55	0.85
N	10	10	10	10
Period: Week 8				
MEAN	16.4	16.5	15.6*	15.2**
SD	0.59	0.82	0.59	0.61
N	10	10	10	10
Period: Week 13				
MEAN	16.0	15.9	15.5	13.5**
SD	0.64	0.65	1.02	1.07
N	9	10	9	10
Period: Week 16				
MEAN	16.1	15.9	16.0	15.6
SD	0.76	0.59	1.34	0.38
N	10	9	9	10
Period: Week 21				
MEAN	16.5	16.3	16.2	16.3
SD	0.58	0.72	0.48	0.76
N	10	10	10	9
Period: Week 27				
MEAN	15.9	15.7	15.5	15.6
SD	0.61	0.67	0.42	0.54
N	10	10	10	9

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

Table 14.3

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Hematocrit

STUDY ID: 098
ABBR: HCT

SEX: FEMALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	42.8	42.0	41.1	36.2**	
SD	1.36	1.82	1.69	2.01	
N	10	10	10	10	
Period: Week 4					
MEAN	43.3	43.6	41.9	40.4**	
SD	1.51	2.04	1.41	2.50	
N	10	10	10	10	
Period: Week 8					
MEAN	43.9	44.8	42.4	41.6*	
SD	1.27	2.50	1.41	1.80	
N	10	10	10	10	
Period: Week 13					
MEAN	43.1	43.3	42.1	37.2**	
SD	1.51	2.14	2.37	3.85	
N	9	10	9	10	
Period: Week 16					
MEAN	43.3	42.8	43.2	43.0	
SD	1.92	1.72	3.01	1.10	
N	10	9	9	10	
Period: Week 21					
MEAN	45.1	45.4	44.6	44.5	
SD	1.88	2.36	1.37	1.78	
N	10	10	10	9	
Period: Week 27					
MEAN	43.1	43.1	42.6	42.4	
SD	2.08	1.96	1.25	1.65	
N	10	10	10	9	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 098 SEX: FEMALE
ABBR: MCV UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	58.9	59.7	58.9	58.6	
SD	1.66	2.35	1.34	1.02	
N	10	10	10	10	
Period: Week 4					
MEAN	58.6	59.5	60.1	58.9	
SD	1.91	2.31	1.24	1.89	
N	10	10	10	10	
Period: Week 8					
MEAN	55.9	57.7*	58.5**	55.2	
SD	1.44	1.91	1.30	1.55	
N	10	10	10	10	
Period: Week 13					
MEAN	54.8	56.4	58.2**	54.4	
SD	1.36	2.28	1.41	2.67	
N	9	10	9	10	
Period: Week 16					
MEAN	56.4	57.6	58.5	57.0	
SD	1.53	2.32	1.83	2.30	
N	10	9	9	10	
Period: Week 21					
MEAN	55.7	56.9	55.8	53.6*	
SD	1.12	2.18	1.33	1.46	
N	10	10	10	9	
Period: Week 27					
MEAN	55.3	56.7	55.1	54.6	
SD	1.57	3.60	1.39	1.66	
N	10	10	10	9	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemoglobin

STUDY ID: 098
ABBR: TMCH

SEX: FEMALE
UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	21.7	21.8	21.6	21.2	
SD	0.69	0.84	0.53	0.65	
N	10	10	10	10	
Period: Week 4					
MEAN	21.3	21.6	21.9	20.6	
SD	0.59	0.83	0.63	0.78	
N	10	10	10	10	
Period: Week 8					
MEAN	20.8	21.2	21.5	20.1	
SD	0.63	0.79	0.69	1.00	
N	10	10	10	10	
Period: Week 13					
MEAN	20.3	20.7	21.5*	19.9	
SD	0.58	0.86	0.68	1.20	
N	9	10	9	10	
Period: Week 16					
MEAN	21.0	21.4	21.6	20.8	
SD	0.72	1.17	0.70	0.74	
N	10	9	9	10	
Period: Week 21					
MEAN	20.4	20.5	20.2	19.7	
SD	0.57	0.78	0.70	0.69	
N	10	10	10	9	
Period: Week 27					
MEAN	20.5	20.6	20.1	20.1	
SD	0.73	1.22	0.51	0.78	
N	10	10	10	9	

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemo. Conc.

STUDY ID: 098
ABBR: TMCHC

SEX: FEMALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	36.8	36.6	36.7	36.2	
SD	0.63	0.62	0.63	0.78	
N	10	10	10	10	
Period: Week 4					
MEAN	36.4	36.2	36.5	34.9**	
SD	0.47	0.47	0.73	0.53	
N	10	10	10	10	
Period: Week 8					
MEAN	37.3	36.8	36.8	36.4	
SD	0.73	0.62	0.83	1.13	
N	10	10	10	10	
Period: Week 13					
MEAN	37.1	36.7	36.9	36.6	
SD	0.85	0.54	0.81	2.89	
N	9	10	9	10	
Period: Week 16					
MEAN	37.1	37.2	36.9	36.4	
SD	1.09	1.14	0.87	0.76	
N	10	9	9	10	
Period: Week 21					
MEAN	36.6	35.9	36.2	36.7	
SD	0.58	0.71	0.92	0.74	
N	10	10	10	9	
Period: Week 27					
MEAN	37.0	36.4	36.5	36.8	
SD	0.76	0.33	0.48	0.66	
N	10	10	10	9	

**-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Reticulocytes Count

STUDY ID: 098
ABBR: RETICS

SEX: FEMALE
UNITS: % RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1.2	1.2	0.7	3.5**	
SD	0.72	0.67	0.58	1.27	
N	10	10	10	10	
Period: Week 4					
MEAN	1.0	1.0	1.5	2.2*	
SD	0.57	0.52	0.97	1.36	
N	10	10	10	10	
Period: Week 8					
MEAN	0.4	0.6	1.0**	1.6**	
SD	0.22	0.25	0.39	0.44	
N	10	10	10	10	
Period: Week 13					
MEAN	0.8	0.7	0.9	2.6**	
SD	0.29	0.28	0.46	1.55	
N	9	10	9	9	
Period: Week 16					
MEAN	0.6	0.5	0.7	0.9	
SD	0.31	0.47	0.45	0.51	
N	10	9	9	10	
Period: Week 21					
MEAN	0.3	0.4	0.4	0.3	
SD	0.24	0.32	0.21	0.18	
N	10	10	10	9	
Period: Week 27					
MEAN	0.6	0.6	0.3	0.5	
SD	0.35	0.56	0.26	0.37	
N	10	10	10	9	

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Nucleated Red Cells

STUDY ID: 098
ABBR: NRBC

SEX: FEMALE
UNITS: COUNT

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.3	
N	10	10	10	10	
Period: Week 4					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.0	
N	10	10	10	10	
Period: Week 8					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.3	
N	10	10	10	10	
Period: Week 13					
MEAN	0	0	0	0	
SD	0.0	0.0	0.3	0.0	
N	9	10	9	9	
Period: Week 16					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.0	
N	10	9	9	10	
Period: Week 21					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.0	
N	10	10	10	9	
Period: Week 27					
MEAN	0	0	0	0	
SD	0.0	0.0	0.0	0.0	
N	10	10	10	9	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Heinz Bodies

STUDY ID: 098
ABBR: HB

SEX: FEMALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.0	0.0	0.1	1.7**	
SD	0.00	0.06	0.13	0.95	
N	10	10	10	10	
Period: Week 4					
MEAN	0.1	0.2	0.3	0.4	
SD	0.16	0.30	0.43	0.39	
N	10	10	10	10	
Period: Week 8					
MEAN	0.1	0.1	0.1	0.2	
SD	0.20	0.15	0.18	0.39	
N	10	10	10	10	
Period: Week 13					
MEAN	0.0	0.0	0.1	0.7**	
SD	0.00	0.04	0.23	0.63	
N	9	10	9	9	
Period: Week 16					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	9	9	10	
Period: Week 21					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	9	
Period: Week 27					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.06	0.00	0.00	
N	10	10	10	9	

**-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: % Methemoglobin

STUDY ID: 098
ABBR: %METHGB

SEX: FEMALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.5	0.5	0.9	12.9**	
SD	0.31	0.35	0.42	1.95	
N	10	10	10	10	
Period: Week 4					
MEAN	0.5	0.6	2.5**	8.1**	
SD	0.27	0.42	0.75	1.96	
N	10	10	10	10	
Period: Week 8					
MEAN	0.7	0.6	4.2**	9.2**	
SD	0.29	0.39	1.04	2.40	
N	10	10	10	10	
Period: Week 13					
MEAN	0.6	0.6	4.7**	12.2**	
SD	0.60	0.29	1.45	2.57	
N	9	10	9	10	
Period: Week 16					
MEAN	0.5	0.3	0.4	1.4**	
SD	0.47	0.22	0.58	0.80	
N	10	9	9	10	
Period: Week 21					
MEAN	0.6	0.5	0.7	0.7	
SD	0.25	0.25	0.41	0.27	
N	10	10	10	9	
Period: Week 27					
MEAN	0.7	0.9	0.8	0.7	
SD	0.26	0.32	0.31	0.45	
N	10	10	10	9	

**-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Platelets

STUDY ID: 098
ABBR: PLT

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1217	1305	1254	1280	
SD	134.6	172.3	189.4	286.3	
N	10	10	10	10	
Period: Week 4					
MEAN	1170	1232	1221	1176	
SD	101.6	209.7	87.5	184.0	
N	10	10	10	10	
Period: Week 8					
MEAN	1030	1116	1072	1046	
SD	166.7	112.7	90.2	167.7	
N	10	10	10	10	
Period: Week 13					
MEAN	983	1069	1078	872	
SD	114.0	174.5	159.8	283.0	
N	9	10	9	10	
Period: Week 16					
MEAN	967	1032	975	996	
SD	137.7	162.9	129.1	147.7	
N	10	9	9	10	
Period: Week 21					
MEAN	938	1004	1017	971	
SD	160.3	243.2	127.1	135.2	
N	10	10	10	9	
Period: Week 27					
MEAN	981	1027	1027	932	
SD	106.3	116.1	71.1	110.6	
N	10	10	10	9	

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Act. Partial Thrombo. Time

STUDY ID: 098
ABBR: APTT

SEX: FEMALE
UNITS: sec

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0 mg base/kg/day
Period: Week 14				
MEAN	15.5	14.6	13.6	12.3*
SD	2.07	1.97	2.37	3.25
N	10	10	10	10
Period: Week 27				
MEAN	12.8	13.5	13.7	15.3
SD	2.05	2.65	2.64	1.84
N	10	10	10	9

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Leukocytes

STUDY ID: 098 SEX: FEMALE
ABBR: WBC UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	15.7	17.6	17.4	25.8**	
SD	3.23	4.90	3.23	5.98	
N	10	10	10	10	
Period: Week 4					
MEAN	11.6	15.5	17.2*	21.5**	
SD	2.93	3.52	6.03	5.21	
N	10	10	10	10	
Period: Week 8					
MEAN	10.4	13.6	16.2**	22.4**	
SD	2.65	2.78	4.93	4.62	
N	10	10	10	10	
Period: Week 13					
MEAN	10.7	11.2	14.0	23.0**	
SD	1.93	1.59	3.68	5.25	
N	9	10	9	10	
Period: Week 16					
MEAN	9.0	10.8	9.2	12.9**	
SD	2.83	1.05	2.49	3.03	
N	10	9	9	10	
Period: Week 21					
MEAN	9.3	10.1	9.6	10.8	
SD	2.31	1.57	1.95	1.47	
N	10	10	10	9	
Period: Week 27					
MEAN	9.2	9.6	10.0	9.2	
SD	1.30	1.89	2.01	1.81	
N	10	10	10	9	

WBC corrected for NRBC = or > 10
**-Significant Difference from Control P < .01
*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: M. Neutrophils

STUDY ID: 098
ABBR: M. Neutrop

SEX: FEMALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	2.1	2.0	2.3	4.7**	
SD	0.89	1.19	1.24	1.08	
N	10	10	10	10	
Period: Week 4					
MEAN	1.3	1.6	3.1**	3.2**	
SD	0.45	0.85	1.84	1.36	
N	10	10	10	10	
Period: Week 8					
MEAN	1.4	1.4	3.5**	2.5	
SD	0.82	0.69	1.59	0.88	
N	10	10	10	10	
Period: Week 13					
MEAN	1.9	1.0	2.9*	3.4**	
SD	0.84	0.48	0.71	1.22	
N	9	10	9	9	
Period: Week 16					
MEAN	1.3	1.8	2.0	2.5**	
SD	0.69	0.93	1.00	0.81	
N	10	9	9	10	
Period: Week 21					
MEAN	1.4	1.3	1.2	1.9	
SD	0.52	0.69	0.57	0.78	
N	10	10	10	9	
Period: Week 27					
MEAN	1.6	1.8	1.8	1.5	
SD	1.29	0.99	0.61	0.76	
N	10	10	10	9	

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

**-Significant Difference from Control P < .01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: I. Neutrophils

STUDY IO: 098
ABBR: I. Neutrop

SEX: FEMALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	1.4	0.0	1.8	0.0	
SD	4.49	0.00	5.76	0.00	
N	10	10	10	10	
Period: Week 4					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.03	0.00	0.00	
N	10	10	10	10	
Period: Week 8					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 13					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	9	10	9	9	
Period: Week 16					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	9	9	10	
Period: Week 21					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	9	
Period: Week 27					
MEAN	0.2	0.0	0.0	0.0	
SD	0.70	0.00	0.00	0.00	
N	10	10	10	9	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Lymphocytes

STUDY ID: 098
ABBR: Lymphocyte

SEX: FEMALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0 mg base/kg/day
Period: Week 2				
MEAN	11.6	15.3	12.8	19.2**
SD	4.71	4.32	5.10	5.22
N	10	10	10	10
Period: Week 4				
MEAN	9.7	13.3	13.5	15.8**
SD	2.79	3.04	4.30	4.67
N	10	10	10	10
Period: Week 8				
MEAN	8.4	11.5	12.0	17.1**
SD	2.36	2.62	4.37	4.39
N	10	10	10	10
Period: Week 13				
MEAN	8.4	9.8	10.4	17.2**
SD	1.35	1.51	4.04	4.32
N	9	10	9	9
Period: Week 16				
MEAN	7.3	8.5	6.8	9.9*
SD	2.27	1.37	1.55	2.15
N	10	9	9	10
Period: Week 21				
MEAN	7.5	8.4	8.0	8.3
SD	2.08	1.46	2.16	1.73
N	10	10	10	9
Period: Week 27				
MEAN	6.2	7.3	7.7	7.1
SD	2.51	1.45	2.30	1.84
N	10	10	10	9

WBC corrected for NRBC = or > 10

**-Significant Difference from Control P < .01

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Monocytes

STUDY ID: 098
ABBR: Monocytes

SEX: FEMALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.4	0.2	0.3	1.8**	
SD	0.55	0.19	0.31	0.68	
N	10	10	10	10	
Period: Week 4					
MEAN	0.5	0.5	0.4	2.3**	
SD	0.43	0.41	0.45	0.87	
N	10	10	10	10	
Period: Week 8					
MEAN	0.6	0.5	0.6	2.8**	
SD	0.26	0.28	0.41	1.98	
N	10	10	10	10	
Period: Week 13					
MEAN	0.3	0.3	0.5	2.8**	
SD	0.22	0.30	0.31	1.32	
N	9	10	9	9	
Period: Week 16					
MEAN	0.3	0.3	0.4	0.4	
SD	0.22	0.27	0.27	0.35	
N	10	9	9	10	
Period: Week 21					
MEAN	0.3	0.3	0.3	0.3	
SD	0.18	0.18	0.26	0.24	
N	10	10	10	9	
Period: Week 27					
MEAN	1.1	0.4	0.4	0.4	
SD	2.14	0.21	0.30	0.19	
N	10	10	10	9	

WBC corrected for NRBC = or > 10

**-Significant Difference from Control P < .01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Eosinophils

STUDY ID: 098
ABBR: Eosinophil

SEX: FEMALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.1	0.1	0.2	0.1	
SD	0.14	0.12	0.13	0.16	
N	10	10	10	10	
Period: Week 4					
MEAN	0.1	0.2	0.2	0.2	
SD	0.09	0.25	0.15	0.25	
N	10	10	10	10	
Period: Week 8					
MEAN	0.1	0.2	0.1	0.1	
SD	0.09	0.20	0.11	0.09	
N	10	10	10	10	
Period: Week 13					
MEAN	0.1	0.1	0.2	0.0	
SD	0.07	0.16	0.16	0.07	
N	9	10	9	9	
Period: Week 16					
MEAN	0.1	0.1	0.1	0.1	
SD	0.13	0.05	0.07	0.16	
N	10	9	9	10	
Period: Week 21					
MEAN	0.1	0.1	0.1	0.2	
SD	0.09	0.16	0.10	0.17	
N	10	10	10	9	
Period: Week 27					
MEAN	0.1	0.1	0.1	0.1	
SD	0.05	0.10	0.11	0.14	
N	10	10	10	9	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Basophils

STUDY ID: 098
ABBR: Basophils

SEX: FEMALE
UNITS: 10^3/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

GROUP(s):	0	0.5	6.0	18.0	mg base/kg/day
Period: Week 2					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 4					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 8					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	10	
Period: Week 13					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	9	10	9	9	
Period: Week 16					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	9	9	10	
Period: Week 21					
MEAN	0.0	0.0	0.0	0.0	
SD	0.00	0.00	0.00	0.00	
N	10	10	10	9	
Period: Week 27					
MEAN	0.0	0.0	0.0	0.0	
SD	0.06	0.00	0.00	0.00	
N	10	10	10	9	

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 098
SEX: MALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
Adrenals (% BODY WEIGHT)					
	MEAN	0.013	0.012	0.015	0.015
	SD	0.0019	0.0016	0.0040	0.0041
	N	10	10	10	5
Brain (% BODY WEIGHT)					
	MEAN	0.418	0.420	0.498**	0.540**
	SD	0.0386	0.0328	0.0328	0.0397
	N	10	10	10	5
Heart (% BODY WEIGHT)					
	MEAN	0.307	0.332	0.368**	0.438**
	SD	0.0199	0.0326	0.0478	0.0482
	N	10	10	10	5
Kidneys (% BODY WEIGHT)					
	MEAN	0.760	0.796	0.943**	1.050**
	SD	0.0604	0.0679	0.0859	0.1712
	N	10	10	10	5
Liver (% BODY WEIGHT)					
	MEAN	3.128	3.365	3.803**	4.312**
	SD	0.2674	0.2837	0.4127	0.3720
	N	10	10	10	5
Spleen (% BODY WEIGHT)					
	MEAN	0.154	0.171	0.315**	0.586**
	SD	0.0180	0.0203	0.0545	0.0924
	N	10	10	10	5
Testes w/Epidid. (% BODY WEIGHT)					
	MEAN	1.029	1.000	1.131	1.372**
	SD	0.0814	0.0786	0.2067	0.0464
	N	10	10	10	5

(1)-0 mg base/kg/day
(2)-0.5 mg base/kg/day
(3)-6.0 mg base/kg/day
(4)-18.0 mg base/kg/day
** - Significant difference P<.01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 098
SEX: MALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
Adrenals (% BODY WEIGHT)					
	MEAN	0.013	0.011	0.013	0.012
	SD	0.0023	0.0033	0.0041	0.0029
	N	10	10	10	10
Brain (% BODY WEIGHT)					
	MEAN	0.363	0.367	0.354	0.385
	SD	0.0360	0.0359	0.0431	0.0351
	N	10	10	10	10
Heart (% BODY WEIGHT)					
	MEAN	0.300	0.294	0.287	0.318
	SD	0.0152	0.0201	0.0188	0.0330
	N	10	10	10	10
Kidneys (% BODY WEIGHT)					
	MEAN	0.722	0.718	0.734	0.774
	SD	0.0490	0.0676	0.0895	0.1045
	N	10	10	10	10
Liver (% BODY WEIGHT)					
	MEAN	3.245	2.984	3.288	3.231
	SD	0.2758	0.3628	0.4150	0.4902
	N	10	10	10	10
Spleen (% BODY WEIGHT)					
	MEAN	0.140	0.143	0.146	0.227**
	SD	0.0128	0.0167	0.0212	0.0342
	N	10	10	10	10
Testes w/Epidid. (% BODY WEIGHT)					
	MEAN	0.908	0.950	0.894	0.987
	SD	0.1118	0.0560	0.1155	0.1075
	N	10	10	10	10

(1)-0 mg base/kg/day
(2)-0.5 mg base/kg/day
(3)-6.0 mg base/kg/day
(4)-18.0 mg base/kg/day
** - Significant difference P<.01

Table 16

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY ABSOLUTE

STUDY: 098
SEX: MALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
BODY WEIGHT (G)	MEAN	512.8	515.0	425.9**	384.3**
	SD	42.24	50.10	35.69	37.56
	N	10	10	10	5
Adrenals (pr) (G)	MEAN	0.066	0.059	0.062	0.059
	SD	0.0103	0.0086	0.0175	0.0203
	N	10	10	10	5
Brain (G)	MEAN	2.129	2.148	2.110	2.067
	SD	0.1014	0.0844	0.0897	0.1439
	N	10	10	10	5
Heart (G)	MEAN	1.571	1.700	1.566	1.682
	SD	0.0922	0.1589	0.2444	0.2267
	N	10	10	10	5
Kidneys (pr) (G)	MEAN	3.879	4.070	4.016	4.008
	SD	0.2336	0.1885	0.5086	0.5701
	N	10	10	10	5
Liver (G)	MEAN	16.044	17.354	16.261	16.548
	SD	1.9742	2.3152	2.7079	1.8732
	N	10	10	10	5
Spleen (G)	MEAN	0.785	0.882	1.338**	2.258**
	SD	0.0962	0.1368	0.2457	0.4491
	N	10	10	10	5
Testes w/Epidid. (pr) (G)	MEAN	5.257	5.134	4.796	5.271
	SD	0.3722	0.4775	0.7868	0.5402
	N	10	10	10	5

(1)-0 mg base/kg/day
(2)-0.5 mg base/kg/day
(3)-6.0 mg base/kg/day
(4)-18.0 mg base/kg/day
** - Significant difference P<.01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY ABSOLUTE

STUDY: 098
SEX: MALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1M	(2) 2M	(3) 3M	(4) 4M
BODY WEIGHT (G)					
	MEAN	604.6	590.0	594.5	552.3
	SD	67.22	50.76	66.07	41.97
	N	10	10	10	10
Adrenals (pr) (G)					
	MEAN	0.076	0.066	0.073	0.068
	SD	0.0158	0.0158	0.0200	0.0162
	N	10	10	10	10
Brain (G)					
	MEAN	2.172	2.151	2.084	2.115
	SD	0.0813	0.1032	0.1456	0.1038
	N	10	10	10	10
Heart (G)					
	MEAN	1.816	1.731	1.697	1.752
	SD	0.2657	0.1827	0.1190	0.1669
	N	10	10	10	10
Kidneys (pr) (G)					
	MEAN	4.355	4.239	4.323	4.268
	SD	0.4858	0.5789	0.3226	0.6224
	N	10	10	10	10
Liver (G)					
	MEAN	19.714	17.713	19.574	17.831
	SD	3.5162	3.2556	3.5524	2.8562
	N	10	10	10	10
Spleen (G)					
	MEAN	0.848	0.845	0.868	1.247**
	SD	0.1385	0.1156	0.1594	0.1851
	N	10	10	10	10
Testes w/Epidid. (pr) (G)					
	MEAN	5.434	5.584	5.273	5.414
	SD	0.3955	0.3565	0.5471	0.3236
	N	10	10	10	10

(1)-0 mg base/kg/day
(2)-0.5 mg base/kg/day
(3)-6.0 mg base/kg/day
(4)-18.0 mg base/kg/day
** - Significant difference P<.01

Table 17

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 098
SEX: FEMALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:		(5) 1F	(6) 2F	(7) 3F	(8) 4F
Adrenals (% BODY WEIGHT)					
	MEAN	0.026	0.028	0.034*	0.038**
	SD	0.0049	0.0070	0.0068	0.0053
	N	10	10	10	10
Brain (% BODY WEIGHT)					
	MEAN	0.735	0.735	0.781	0.815**
	SD	0.0635	0.0783	0.0325	0.0376
	N	10	10	10	10
Heart (% BODY WEIGHT)					
	MEAN	0.355	0.345	0.370	0.408*
	SD	0.0404	0.0343	0.0245	0.0510
	N	10	10	10	10
Kidneys (% BODY WEIGHT)					
	MEAN	0.782	0.783	0.922**	0.964**
	SD	0.0688	0.0781	0.0518	0.1146
	N	10	10	10	10
Liver (% BODY WEIGHT)					
	MEAN	3.204	3.146	3.599**	4.059**
	SD	0.3330	0.2620	0.1125	0.2913
	N	10	10	10	10
Ovaries (% BODY WEIGHT)					
	MEAN	0.044	0.049	0.059*	0.066**
	SD	0.0077	0.0118	0.0106	0.0144
	N	10	10	10	10
Spleen (% BODY WEIGHT)					
	MEAN	0.194	0.203	0.321**	0.593**
	SD	0.0358	0.0362	0.0581	0.0913
	N	10	10	10	10

(5)-0 mg base/kg/day
(6)-0.5 mg base/kg/day
(7)-6.0 mg base/kg/day
(8)-18.0 mg base/kg/day
* - Significant difference P<.05
** - Significant difference P<.01

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 098
SEX: FEMALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
Adrenals (% BODY WEIGHT)					
	MEAN	0.027	0.027	0.028	0.027
	SD	0.0076	0.0065	0.0051	0.0083
	N	10	10	10	9
Brain (% BODY WEIGHT)					
	MEAN	0.646	0.645	0.678	0.690
	SD	0.0686	0.0783	0.0434	0.0390
	N	10	10	10	9
Heart (% BODY WEIGHT)					
	MEAN	0.356	0.355	0.349	0.380
	SD	0.0412	0.0324	0.0262	0.0394
	N	10	10	10	9
Kidneys (% BODY WEIGHT)					
	MEAN	0.719	0.724	0.761	0.865**
	SD	0.0748	0.0505	0.0679	0.0765
	N	10	10	10	9
Liver (% BODY WEIGHT)					
	MEAN	2.897	2.889	3.129	3.102
	SD	0.1915	0.2838	0.3212	0.2650
	N	10	10	10	9
Ovaries (% BODY WEIGHT)					
	MEAN	0.035	0.034	0.037	0.035
	SD	0.0053	0.0077	0.0095	0.0097
	N	10	10	10	9
Spleen (% BODY WEIGHT)					
	MEAN	0.163	0.168	0.184	0.274**
	SD	0.0208	0.0311	0.0172	0.0451
	N	10	10	10	9

(5)-0 mg base/kg/day
(6)-0.5 mg base/kg/day
(7)-6.0 mg base/kg/day
(8)-18.0 mg base/kg/day
** - Significant difference P<.01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605 WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY ABSOLUTE

STUDY: 098
SEX: FEMALE

ALL FATES DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
BODY WEIGHT (G)	MEAN	273.7	270.9	249.8**	236.3**
	SD	21.33	18.91	12.44	14.32
	N	10	10	10	10
Adrenals (pr) (G)	MEAN	0.072	0.074	0.084	0.088
	SD	0.0135	0.0178	0.0175	0.0128
	N	10	10	10	10
Brain (G)	MEAN	2.000	1.979	1.947	1.923
	SD	0.0696	0.1177	0.0403	0.0806
	N	10	10	10	10
Heart (G)	MEAN	0.967	0.933	0.924	0.964
	SD	0.0888	0.0857	0.0845	0.1437
	N	10	10	10	10
Kidneys (pr) (G)	MEAN	2.132	2.112	2.301	2.276
	SD	0.1549	0.1727	0.1436	0.2868
	N	10	10	10	10
Liver (G)	MEAN	8.758	8.503	8.993	9.594
	SD	1.0305	0.7231	0.6026	0.9103
	N	10	10	10	10
Ovaries (G)	MEAN	0.121	0.132	0.147	0.155
	SD	0.0223	0.0278	0.0293	0.0376
	N	10	10	10	10
Spleen (G)	MEAN	0.528	0.552	0.804**	1.402**
	SD	0.0919	0.1250	0.1578	0.2530
	N	10	10	10	10

(5)-0 mg base/kg/day
(6)-0.5 mg base/kg/day
(7)-6.0 mg base/kg/day
(8)-18.0 mg base/kg/day
** - Significant difference P<.01

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR 238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

ORGAN WEIGHT SUMMARY ABSOLUTE

STUDY: 098
SEX: FEMALE

ALL FATES DAYS: 182-183 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1F	(6) 2F	(7) 3F	(8) 4F
BODY WEIGHT (G)					
	MEAN	313.8	309.5	300.6	288.9
	SD	28.70	37.61	18.59	19.92
	N	10	10	10	9
Adrenals (pr) (G)					
	MEAN	0.082	0.082	0.084	0.079
	SD	0.0199	0.0181	0.0165	0.0226
	N	10	10	10	9
Brain (G)					
	MEAN	2.012	1.973	2.033	1.988
	SD	0.1028	0.1059	0.0765	0.0977
	N	10	10	10	9
Heart (G)					
	MEAN	1.112	1.093	1.047	1.094
	SD	0.1113	0.1081	0.0811	0.0844
	N	10	10	10	9
Kidneys (pr) (G)					
	MEAN	2.241	2.237	2.290	2.503
	SD	0.1380	0.2911	0.2618	0.3281
	N	10	10	10	9
Liver (G)					
	MEAN	9.067	8.933	9.426	8.976
	SD	0.7505	1.3209	1.3177	1.1219
	N	10	10	10	9
Ovaries (G)					
	MEAN	0.109	0.104	0.111	0.102
	SD	0.0185	0.0272	0.0296	0.0311
	N	10	10	10	9
Spleen (G)					
	MEAN	0.510	0.513	0.552	0.788**
	SD	0.0639	0.0770	0.0374	0.1256
	N	10	10	10	9

(5)-0 mg base/kg/day
(6)-0.5 mg base/kg/day
(7)-6.0 mg base/kg/day
(8)-18.0 mg base/kg/day
** - Significant difference P<.01

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

Table 19

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR238605
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

Summary of Microscopic Lesions[a]

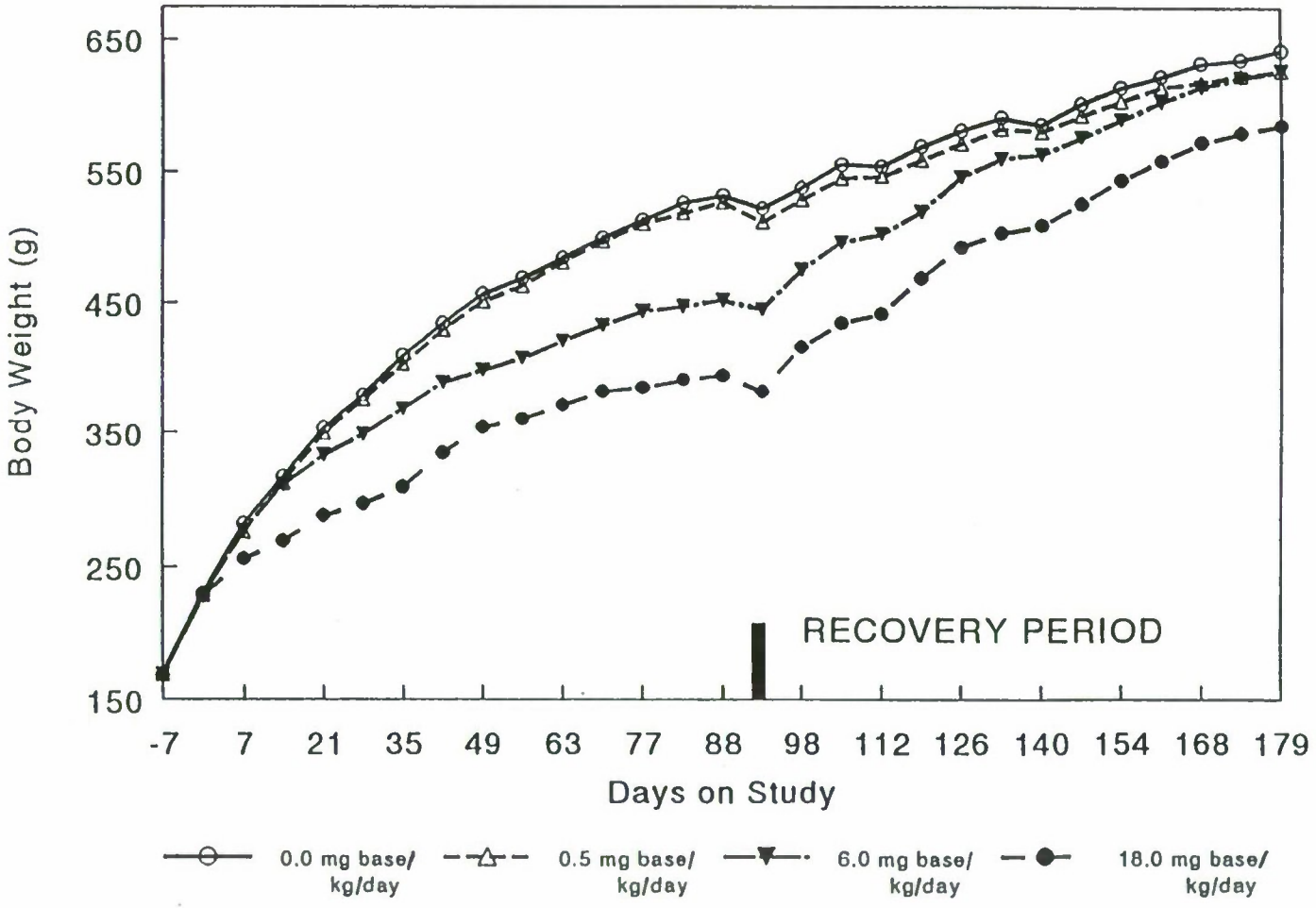
		Dose (mg base/kg/day)							
ORGAN - lesion	Sex	0	0.5	6.0	18.0	0 - R	0.5 - R	6.0 - R	18.0 - R
LUNGS - Alveolar proteinosis	M	0/10 (0.00)	0/10 (0.00)	10/10 (1.70)	5/5 (2.80)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)
	F	0/10 (0.00)	0/10 (0.00)	10/10 (1.60)	10/10 (2.20)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/9 (0.00)
- Chronic inflammation	M	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/5 (0.00)	0/10 (0.00)	0/10 (0.00)	5/10 (0.50)	1/10 (0.20)
	F	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	7/10 (1.10)	5/9 (0.67)
- Hemosiderin pigment	M	1/10 (0.20)	0/10 (0.00)	0/10 (0.00)	0/5 (0.00)	0/10 (0.00)	1/10 (0.10)	7/10 (0.80)	8/10 (0.80)
	F	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	8/10 (1.20)	9/9 (1.11)
KIDNEY - Hemoglobin nephrosis	M	0/10 (0.00)	0/10 (0.00)	5/10 (0.50)	5/5 (2.20)	0/10 (0.00)	-	-	0/10 (0.00)
	F	0/10 (0.00)	0/10 (0.00)	4/10 (0.40)	10/10 (1.50)	0/10 (0.00)	-	-	0/9 (0.00)
- Hemosiderin pigment	M	0/10 (0.00)	0/10 (0.00)	1/10 (0.10)	5/5 (2.20)	0/10 (0.00)	-	-	2/10 (0.20)
	F	0/10 (0.00)	0/10 (0.00)	2/10 (0.20)	10/10 (2.20)	0/10 (0.00)	-	-	1/9 (0.11)
BONE MARROW - Hemosiderin pigment	M	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	2/5 (0.40)	0/10 (0.00)	-	-	0/10 (0.00)
	F	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	5/10 (0.50)	0/10 (0.00)	-	-	0/9 (0.00)
SPLEEN - Hyperplasia	M	0/10 (0.00)	0/10 (0.00)	4/10 (0.60)	5/5 (2.20)	0/10 (0.00)	-	-	0/10 (0.00)
	F	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	8/10 (1.50)	0/10 (0.00)	-	-	0/9 (0.00)

[a]Incidence (mean group severity) - Determined by dividing the sum of all severity scores for a finding by the number of tissues examined. See Pathology Report in Appendix 10.

R = Recovery groups

Contract No.: DAMD17-92-C2001
Task Order No.: UIC-5B
UIC/TRL Study No.: 098

FIGURE 1
SUMMARY OF MALE BODY WEIGHTS



DRAFT

FIGURE 2

SUMMARY OF FEMALE BODY WEIGHTS